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Dreschfeld Memorial Volume

CONTAINING AN ACCOUNT
OF THE
LIFE, WORK, AND WRITINGS
OF THE LATE
JULIUS DRESCHFELD M.D. F.R.C.P.
WITH A SERIES OF ORIGINAL ARTICLES
DEDICATED TO HIS MEMORY
BY COLLEAGUES IN THE
UNIVERSITY OF MANCHESTER
AND FORMER PUPILS

Edited by E. M. BROCKBANK M.D. F.R.C.P.

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CONTENTS.

	PAGE
Memoir—Julius Dreschfeld, 1845—1907 - - - -	1
Bibliography of Papers by the late Prof. Dreschfeld - -	10
“Some Malformations of the Human Heart.” A. H. YOUNG, LL.D., F.R.C.S., etc., and ARTHUR ROBINSON, M.D. -	16
“Notes on some of the less Familiar Joint Affections.” G. A. WRIGHT, B.A., M.B. Oxon, F.R.C.S. - - -	27
“The Supervention of Epithelioma upon Lupus Vulgaris.” ROBERT B. WILD, M.D., M.Sc., M.R.C.P. - - -	46
“The Surgical Treatment of Labyrinthine Suppuration.” W. MILLIGAN, M.D. - - - - - - -	57
“Intermittent Limp.” ERNEST S. REYNOLDS, M.D. (Lond.), F.R.C.P. - - - - - - -	63
“Hyperplasia of Superior Maxilla” F. H. WESTMACOTT, B.Sc. (Vict.), F.R.C.S. (Eng.) - - - - -	71
“On the Oral, Laryngeal and Nasal Symptoms of Myx- œdema.” SIEGMUND MORITZ, M.D., M.R.C.P. (Lond.)	78
“The Symptoms due to Cervical Ribs.” WILLIAM THORBURN, F.R.C.S. - - - - - - - -	85
“Malignant Disease of the Body of the Uterus.” ARCHIBALD DONALD, M.A., M.D., C.M. - - - - - -	112
“Cholesterin: some account of its Chemical, Physical, and Biological Relations.” F. CRAVEN MOORE, M.D., M.Sc. (Vict.), M.R.C.P. (Lond.) - - - - - -	124
“Notes on a Case of Phosphorus Poisoning, with some Observations on the Amino-Acid Excretion.” F. H. EDGEWORTH, M.B., D.Sc., and I. WALKER HALL, M.D. -	161
“Cholesterol, Fluid Crystals, and Myelin Forms.” CHARLES POWELL WHITE - - - - - - - -	167
“Gas-containing Cysts or Air-Bladder Tumours.” W. MAIR	186
“On a Case of HæmolympH Glands.” J. LORRAIN SMITH, M.D. - - - - - - - -	203
“A Note on Colourless Fæces without Jaundice.” J. DIXON MANN - - - - - - - -	210
“Case of (?) Tubercular Intra-Ocular Growth.” A. HILL GRIFFITH, M.D. - - - - - - - -	214
“Chronic Joint Disease of Still’s Type.” E. N. CUNLIFFE, M.D., M.R.C.P. - - - - - - - -	217
“Blood Plates.” E. M. BROCKBANK, M.D., F.R.C.P. - -	226
“Pathogenic Properties of and Amount of Dirt Contained in the Milk supplied to the Town of Manchester During the Ten Years 1897 to 1906 Inclusive.” SHERIDAN DELEPINE, M.B., C.M., M.Sc. - - - - -	237

JULIUS DRESCHFELD.

1845—1907.

ON the 13th of June, 1907, Manchester lost one of her most renowned citizens, the Victoria University one of her most prominent teachers, the North of England its most eminent physician.

Julius Dreschfeld died on that date. Though he had been afflicted for some years with lameness—due to some obscure spinal trouble—his undiminished and unimpaired mental activity and the cheerful view he himself took of his condition had calmed any misgivings or uneasiness which his friends had felt. But after a few days' illness, whilst conversing with a friend, without any sign of pain or discomfort, Dreschfeld suddenly expired.

Julius Dreschfeld was born in October, 1845, at Niederwern, in Bavaria. He received his early education in Bamberg. In 1861 he came to Manchester, where his relatives were living, and he began his studies at the Owens College, then situated in Quay Street. Even when a boy he showed unusual abilities; in a few years, for instance, he mastered the language of his then adopted country to such an extent that he gained a prize in English; he also gained the Dalton Chemical Prize in 1863, and the Dalton Junior Mathematical Scholarship in 1864. He continued the study of medicine at the Royal School of Medicine in Pine Street, Manchester. But he soon left this for the University of Würzburg. The medical school of this University was then at its best; Koelliker was teaching anatomy, embryology, and histology, von Bezold physiology, Virchow had established a school of pathology, and Bamberger, who shortly thereafter went to Vienna, was one of the greatest clinical teachers in Germany. The opportunities offered for

the study of histology, normal and pathological, at the German universities formed one of the distinguishing features between these and the English schools of those days. Dreschfeld availed himself most thoroughly of these opportunities, and thus formed the basis for his future success as a pathologist. In 1867 he took the degree of M.D. in Würzburg with a thesis on the reflex action of the vagus on the blood-pressure, based on experimental investigations carried out under Bezold's direction in the laboratory of this distinguished physiologist. In 1866 Dreschfeld volunteered as assistant surgeon in the sharp and short Prusso-Austrian war; cholera, typhus and typhoid were filling the military hospitals and required the exertions of the medical staffs.

After visiting other German universities, and also that of Paris, Dreschfeld returned, in 1869, to Manchester. He passed the examination of L.R.C.P. London, and began practice in Higher Broughton. In 1872 he removed to Oxford Road. In 1874 he obtained his first public appointment as honorary physician to the Hulme Dispensary, Manchester, and in the following year he was appointed assistant physician to the Manchester Royal Infirmary, and lecturer on pathology at the Owens College. The last two appointments offered unsurpassable opportunities to a man talented like Dreschfeld, who, endowed with an unbounded enthusiasm for work, possessed the keenest powers of observation and quick perception, a most retentive memory and a knowledge with a sound and broad scientific basis. In 1876 he became a Member and in 1883 was elected a Fellow of the Royal College of Physicians of London. In 1882 his success in the teaching of pathology, of which more hereafter, was acknowledged by his election as professor of pathology, and in the following year, on the retirement of Sir William Roberts, he became full physician at the Royal Infirmary.

In spite of the enlarged clinical work thus accruing to him, he continued teaching pathology and pathological histology. The zest with which the study of bacteriology was taken up in these years made Dreschfeld devote a long "holiday" for the purpose of studying bacteriological methods at the fountain

head, at Koch's laboratory. But, feeling that laboratory work demanded more time than he could devote to it, he resigned, in 1892, the chair of pathology, exchanging it for the professorship of medicine. Having since his appointment at the Infirmary devoted much time to clinical teaching, and being in fact the foremost clinical teacher of the school, his previous experience as a teacher of pathology made him a most successful lecturer in medicine, reminding one of E. Wagner, of Leipzig, who also after he had held the professorship of pathology for years, had exchanged it for that of medicine. *Pari passu* with his increased responsibilities his fame as a consulting physician kept increasing, so that for many years he held the busiest consulting practice in the north of England. His renown and his merits were widely recognised by his being chosen President of the Pathological Section of the British Medical Association (1886), Bradshawe Lecturer at the College of Physicians (1887), Examiner in Medicine at the University of Cambridge (1892) and at the Conjoint Board of England (1897), President of the Medical Section of the British Medical Association (1902), and shortly before his death Lumleian Lecturer at the Royal College of Physicians.

In spite of his busy practice and his careful attention to his duties as a hospital physician, a teacher and examiner, Dreschfeld devoted much time to literary work. The appended list of his published writings, prepared by Mr. Clayton, the Librarian of the Manchester Medical Society, shows a record of over one hundred papers, and in addition there must be many others which were read before the Manchester and other medical societies without being printed. He always took a most active interest in the welfare of the Manchester Medical Society, and almost all his more important additions to medical knowledge were announced at its meetings. Moreover, in addition to reading original papers and showing interesting clinical cases before the Medical and Pathological Societies, he frequently brought to their notice important work done abroad. His literary work shows not only his great knowledge of pathology and his extensive clinical experience, but also his wide and accurate reading. Where nearly everything is good, it would be almost invidious to pick

out single instances, but the most important additions to medical knowledge for which we have to thank Dreschfeld are the following.

He was the first to recommend in a medical journal a watery solution of eosin, with subsequent rinsing in water acidulated with acetic acid, for staining histological sections. He found it especially good for nervous tissue, in which the nuclei and nucleoli of the ganglion cells were stained a light pink. The axis cylinders of the nerve fibres and the processes of the ganglion cells were stained in a similar way, whilst the medulla of the nerve fibres was not stained; the areolar tissue took a much deeper tint. He recommended eosin especially for the examination of fresh sections for diagnostic purposes owing to the short time required for staining them. The dye had been used previously in ammonia and potash solution as a histological stain, and had been recommended for staining the salivary and lachrymal glands (*Zeitschrift f. wissenschaft. Mikros. u.f. mikros. Technik.* 1884. Band I., p. 376).

His paper on primary lateral sclerosis was very valuable as it confirmed the clinical observations of Erb and Charcot who had described the symmetrical progressive sclerosis of the lateral columns of the spinal cord which advanced from below upwards. Leyden had begun to doubt the independent existence of such a disease, but Dreschfeld had the opportunity of studying clinically and pathologically a typical case at the Manchester Royal Infirmary. This was the first case of the disease on which a post-mortem examination was made, and Dreschfeld's anatomical findings afforded material support to the views which Erb and Charcot had expressed as a result of their clinical investigations.

He also wrote some important papers on experimental researches in the pathology of pneumonia, on the changes in the spinal cord after amputation of the limbs, on some points in the pathology of cirrhosis of the liver and of acute yellow atrophy, and he made important contributions to the investigation of the course of the fibres of the optic nerve in the brain.

In addition to the description of numerous rarer medical cases, we find, soon after the discovery of the tubercle bacillus, some investigations as to its diagnostic value published in the

British Medical Journal (1883), and recognising the important rôle which bacteriology began to play, an important paper on "Micro-organisms in their Relation to Disease," a paper which was translated into French and Italian. Further important papers "On the Lung Complications of Diabetes," "On Creeping Pneumonia," "On Alcoholic Paralysis," "On the Clinical Diagnosis of Cancer of the Stomach," were published from 1883 to 1886. In the latter year Dreschfeld read the Bradshawe Lecture on "Diabetic Coma" giving most important original observations. In 1890 a publication on "Angina Pectoris" and a paper on "Interstitial Hepatitis," read before the International Medical Congress, deserve special mention. The following years saw a series of publications on numerous subjects, in which rare cases of diseases of the nervous system decidedly predominate, though there are also many papers on other questions. Finally, Dreschfeld's contributions to Clifford Allbutt's *System of Medicine* must be mentioned, viz., the articles on "Infective Endocarditis," "Enteric Fever," "Ulcer of the Stomach and Duodenum," and on "Endocarditis."

Dr. Robert Maguire, who was Dreschfeld's assistant in his pathological work in his earliest days, writes:—

"Dreschfeld's most original piece of scientific work was never published. If it had been pursued it would have been of the utmost importance. In 1882—1883 there was an outburst of hydrophobia in Manchester, several deaths occurring in the Infirmary and others outside. Altogether it fell to Dr. Dreschfeld's demonstrator to make about ten autopsies. Pasteur had then said nothing about hydrophobia. He had just published his work on the "Intensification" and then the "Diminution" of the anthrax poison which led to his results on "Immunisation." Dreschfeld had the idea that the same might be done with hydrophobia, and set to work on the question. The whole of Pasteur's work on the intensification of hydrophobia poisoning by passage through rodents was done at Owens College before a word came from Paris, and this was Dreschfeld's work. At first it took three weeks to kill a rabbit by inoculating it with saliva or blood, but at last a poison was obtained which would kill a rabbit in 12 hours. Dreschfeld had the idea that the

poison lay in the spinal cord, and therefore he kept the spinal cords for some time, and up to a few years ago they were still in the laboratory, and the experiments were recorded in the laboratory book. He proposed that after keeping the cords an emulsion of them should be made and injected into dogs to see if the poison had changed in virulence. Thus was Pasteur's work very closely foreshadowed, but the Vivisection Act of that date stopped the experiments.

“ Thanks really to Dreschfeld Manchester has been better informed of Continental work than any other place in the Kingdom. When he was Assistant Physician he read Kussmaul's observations on lavage of the stomach, and set to work to carry them out for himself. In doing this he forestalled by ten years an eminent and prominent London Physician who took up the same subject and used the method very largely in his practice. This constant study of Continental progress gave Dreschfeld too little time for original thought. For instance, about 1884 he did some work on “ wandering ” pneumonia. He believed that the pneumonia was infectious, but more recent observations have shown that the pneumonia followed some previous infection not then so well understood as is influenza at the present day. Dreschfeld's observations on these cases were most accurate and his descriptions show that he was dealing with the first instances of the then new influenza, but he did not see this, his ideas being prepossessed by the observations of Kussmaul who had worked on similar lines.

“ His first course of lectures in pathology, like many of those which followed, was not ‘ compulsory.’ It was attended by two students, one of whom had to leave at the half-hour to attend another lecture. Dreschfeld told me that he always entered the room with fear lest the one man who remained the whole hour should be kept away by some cause, and the lecture be therefore stopped at half-time, for want of an audience. This, however, never happened.”

Whilst Dreschfeld by his work as a physician and teacher secured the gratitude of his contemporaries, and by his writings a world-wide fame, one paramount service which he rendered to the University to which he was attached, and to medicine

in England in general, deserves special acknowledgment. This is that he was the first at any English medical school to teach systematically pathology and pathological histology, and to secure to these branches of medical knowledge the important rôle which they now possess and ought to possess in the medical curriculum. Not only was Dreschfeld, when appointed in 1882, the first professor of pathology at the Owens College, he was the first professor of pathology in England, for the chair of pathology in Cambridge—(We are indebted to Prof. Woodhead for this information)—was established by Grace on December 6th, 1883, and the first professor was appointed there in 1884. Thus Cambridge was the first university in England to follow the example set by Manchester.

What the state of affairs in regard to the study and teaching of pathology was at this time was aptly and with great moderation put forward by Dreschfeld in his opening address at the Annual Meeting of the British Medical Association in 1886. "Whilst fully admitting," he said, "the vast amount of pathological work done in England, one cannot help feeling that still more would be done, if we had institutes like those on the Continent, and if pathology entered more largely into the curriculum of our medical study. . . . At present we miss systematic instruction in pathology, the lectures are insufficient in numbers, the teaching in the post-mortem rooms is often left to inexperienced demonstrators. . . . There is no separate examination for the various diplomas and degrees" excepting "the University of Cambridge, which has recently established an endowed chair of pathology, and gives due weight to pathology in the medical examination, and the Victoria University, where separate examinations are held, both in general pathology and in pathological anatomy, and where the candidate for the degree has to bring proofs of having studied pathology practically in a laboratory."

(Even in Cambridge, though the professorship in pathology was instituted in 1884, "the examination in special and general pathology which was commenced at the time was conducted in connection with the examination in medicine, but in June, 1898, a special examination in general pathology was instituted, the

special pathology examination still being carried on in connection with the medicine and surgery examination.”—Professor Woodhead.)

It was no doubt due to the exertions of Dreschfeld that this most necessary reform was introduced at the Victoria University, and the example here set followed by other examining boards throughout the kingdom. For those who have studied on the Continent and for the younger generation, it is difficult to realise that the inclusion of pathology as an essential and important part of the medical curriculum should be of such recent date, a reform which within so short a time has contributed largely to the establishment of schools of pathology in England equal to any in the world.

Whilst these were perhaps the main results of Dreschfeld's work as regards the larger medical world, it is almost needless to enlarge upon his more immediate influence on his pupils and his colleagues.

As a teacher or lecturer he was characterised by his wide reading, wonderful memory, vast clinical experience and clear thinking. His classes, lectures, and addresses were all models of lucidity, and were delivered with a facility which showed perfect acquaintance with his subject, and which made difficult problems seem so easy and straightforward to every member of his audience. Any subject which engaged his attention was discussed in great detail, and whilst it may be said with perfect truth that average students require more instruction in broad principles than Dreschfeld was in the habit of giving, it cannot be denied that such a training in the importance of details, as was received in his ward classes or lectures, was a most valuable preparation for future practice.

Dreschfeld impressed students and medical men by his wonderful memory for the smallest details of his previous scientific or clinical experience. He probably never forgot any case which had interested him, and he could recall such cases years afterwards, when he wanted to illustrate a lecture. He also had a fluent knowledge of French and German as well as of English, was an omnivorous reader of medical literature and possessed the power of picking out the most valuable observations which he stored away in his memory and incorporated in his notes for lectures or ward classes.

There is no doubt that the example he set as an arduous, patient and consistent worker, as a most able and still most painstaking and conscientious physician was of the greatest influence to all who came in contact with him. Few medical men indeed there can be in this district who have not learned from him; every consultation was an object lesson in pathology and medicine. Added to this there came his charming modesty, so that even the humblest practitioner felt he was meeting merely a colleague and not the renowned professor.

Of Dreschfeld's private life there is little to say. His time was so fully taken up with the exercise of his profession, his duties as a teacher and his literary work, that there was no room left for other interests. Apart from his fondness for music he had no hobbies. In conversation, even with his most intimate friends, no other than medical subjects could engage his attention for a prolonged time.

He was, above all, a splendid example of an indefatigable worker. Hurrying from consultation to consultation, one railway journey after another, in cold, fog or rain, returning home late in the evening, he would still settle down to literary work often until early morning hours; thus he would forget the toil of the preceding day and not think of the probable hard work of the next. To Dreschfeld his work was everything. Personal comforts he utterly disregarded; the calls of his family or of friendship were also brushed aside when there was work to do, and he even would not give in to the demands for more bodily and mental rest which his failing health during later years must have made more or less urgent. Thus to the end! His mind being perfectly clear, he was, only a few hours before his death, planning out more work and speaking of the experimental researches which he intended to make in regard to the digestion of different foods in the stomach in health and in disease, a subject which he thought of choosing for the Lumleian Lectures; but he felt his increasing weakness, and almost his last words to a friend were: "I am afraid I shall never do it; but never mind, I have done my share; I have had my innings, and a good innings it has been, and I have enjoyed it; let others follow on!" Calmly and contentedly he looked death in the face—swift, painless and sudden the end came. "I feel better, I shall sleep to-night," were his last words.

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SOME MALFORMATIONS OF THE HUMAN HEART.

By

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and

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THE inclusion of a paper dealing with facts which, at present, seem to have little practical bearing, in a volume devoted to the memory of the late Professor Dreschfeld requires no apology, for all who knew him, as we knew him, are aware that he extended the utmost sympathy and support to those who were working with the object of increasing scientific knowledge. He saw clearly that advances could only be made in medicine, as in other sciences, by the accumulation and digestion of facts, remembering that such facts, though apparently useless to-day, frequently become the working capital of to-morrow. We have therefore no hesitation in including in this volume a record of a series of observations which, with others of a similar character, are, we believe, tending towards the solution of some interesting questions with regard to the development of the heart, the elucidation of which may lead to a better appreciation of the peculiarities and capabilities of the organ.

We intend, however, at present merely to register our observations on some interesting malformations, without discussing at any length their bearing on developmental problems; in a future communication we propose to deal with these problems at greater length. The anomalies we record are interesting, both from a clinical point of view, so far as their histories are known, as well as from a pathological and an embryological standpoint, from the latter standpoint in particular, because of their suggestiveness with regard to some obscure points in the development of the organ.

DESCRIPTION OF THE SPECIMENS.

CASE I. Complete absence of the inter-ventricular septum.

This specimen, which occurred in an apparently healthy man of 35 years of age, is, on account of the age of the patient, almost unique. It has already been described by one of ourselves,¹ and we only reproduce an illustration which shows its most salient features; briefly, these are as follows:—There is only a single ventricle. The inter-ventricular septum (septum inferius) is hardly distinguishable; a small ridge, little more than a well-developed “columna carneæ,” is the only representative of the septum. The ventricle, however, is partly divided by an infundibulo-ventricular band into two cavities. The aorta and the pulmonary are transposed.

CASE II. Complete obliteration of the stem of the pulmonary artery. Patent ductus arteriosus from which the right and left pulmonary arteries arise. Imperfect inter-ventricular septum. Patent foramen ovale, etc., in a female child, aged $2\frac{1}{2}$ years.

For the clinical history of this case we are indebted to Dr. Lapage, and for permission to examine and report upon the specimen to Dr. Ashby, who, with his usual kind courtesy, placed it entirely at our disposal.

The patient was first seen by Dr. Lapage when she was two years old. At that time she was fairly well nourished, she was distinctly cyanotic, the extremities of her fingers were clubbed and the external ears showed marked signs of lobulation, a condition which Dr. Ashby finds is not uncommonly associated with imperfect development of the heart. On further examination a loud systolic murmur could be heard over the greater part of the chest, and it was particularly marked to the right of the middle line. When the child reached two and a half years she was seized with broncho-pneumonia, and was sent as an in-patient to the Pendlebury Hospital, where she came under Dr. Ashby's observation, and where she subsequently died.

1. Young, A. H. “Rare Anomaly of the Human Heart: a three-chambered Heart in an Adult, aged 35 years.” *Journal of Anatomy and Physiology*, vol. xli., p. 190.

When the heart was removed at the post-mortem examination it showed signs of general hypertrophy, especially as regards the left ventricle. The veins were unfortunately cut very short, and one or two points in the anatomy of the auricles are therefore less clear than we could desire.

Auricles. Right Auricle. In the removal of the heart a portion of the wall of the auricle was removed, and no trace of the superior vena cava could be found, but from the general appearance of the specimen we doubt if it was ever developed. There is also no definite inferior vena cava, but along the line of union of the auricle and the sinus venosus there is a remnant of a Eustachian valve running towards but not reaching the anterior limb of the annulus ovalis. The sinus venosus is prolonged to the left round the back of the lower part of the left auricle; that is, the original left cornu still exists, and has not been reduced to a coronary sinus. This cornu receives, at its left extremity, a large left superior vena cava which descends obliquely from left to right and from above downwards across the posterior wall of the left auricle. On the septal wall of the auricle in front of the left cornu of the sinus venosus, and separated from the latter by a distinct muscular ridge, is a deep pit-like fossa ovalis (Fig. 2), in the anterior part of which there is a small opening of communication with the left auricle. Immediately behind the ridge which separates the fossa ovalis from the left cornu of the sinus venosus there is a second communicating orifice between the two auricles (Fig. 2) through the lower part of the inter-auricular septum.

Left Auricle. The walls of the left auricle are comparatively thin and the cavity is divided into right-posterior and left-anterior portions by a deep ridge, which corresponds externally with the deep sulcus in which the left superior vena cava lies, and by the projecting floor of the fossa ovalis. The anterior portion communicates with the right auricle in the region of the fossa ovalis, and the margins of the communicating aperture on the left side are situated between radiating muscular bundles similar to those which are so often met with in this region. Towards the left the anterior part of the body of the auricle is prolonged into the auricular appendix.

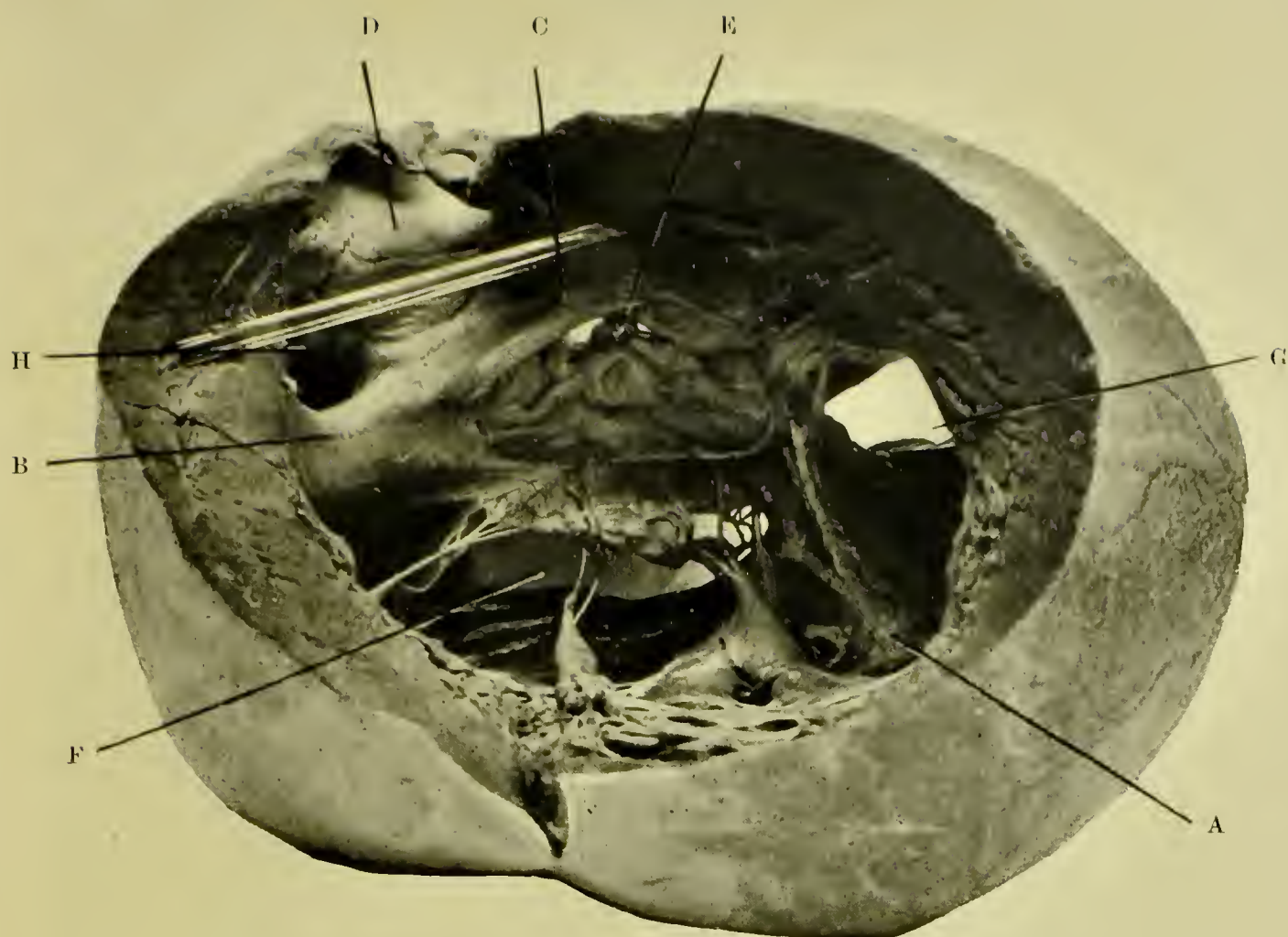


FIG. 1.—The cavity of the common ventricle (from a photograph by Messrs. Flatters & Garnett, Manchester). Part of the anterior wall of the ventricle has been removed and the ventricle opened out laterally; a glass rod is inserted to keep the cavity open.

A, septum inferius (interventricular septum); B and C, parts of infundibulo-ventricular ridge; D, aorta; E, orifice of the pulmonary artery; F, right auriculo-ventricular aperture and tricuspid valve; G, left auriculo-ventricular aperture and mitral valve; H, remains of the infundibular part of the right ventricle, previously described as the remains of the bulbus cordis.

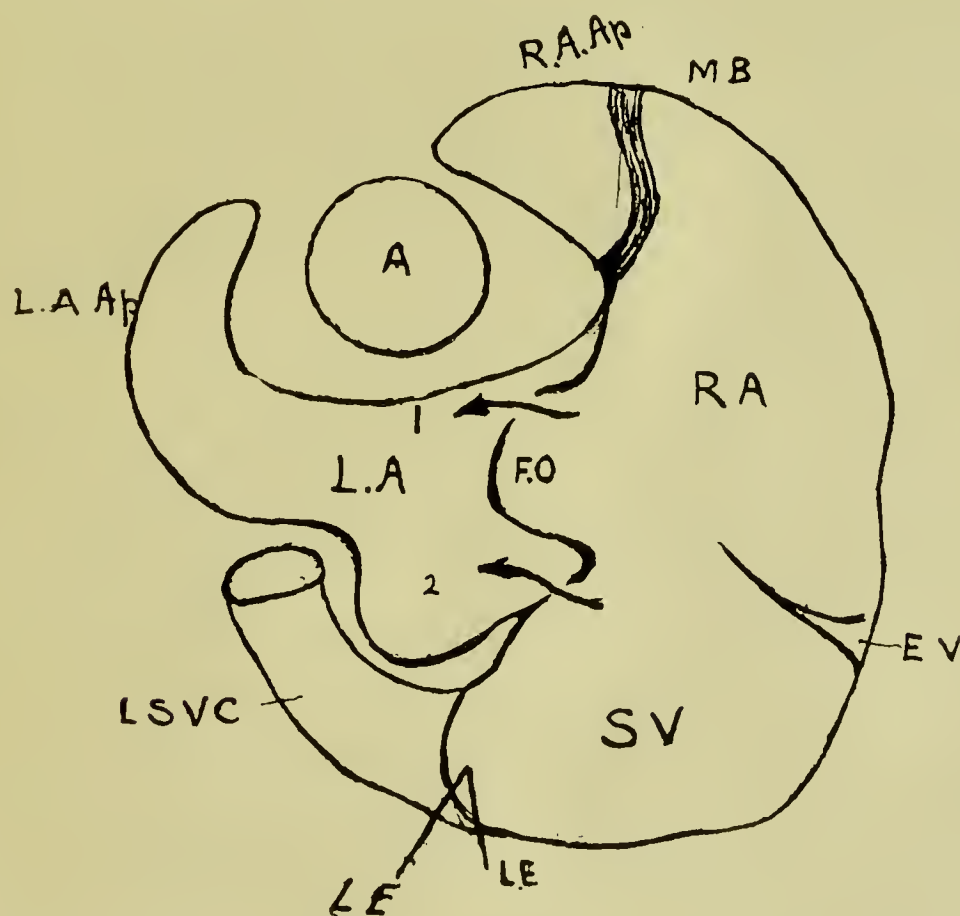


FIG. 2.—Horizontal Section through the auricular part of the Heart of Case II. (Diagrammatic).

- | | | | |
|------|--------------------------|------|---|
| A | Aorta. | LE | Left extension of sinus venosus, or left cornu. |
| EV | Eustachian valve. | LSVC | Left superior vena cava. |
| FO | Fossa ovalis. | MB | Moderator band in right auricle. |
| LA | Left Auricle. | RA | Right auricle. |
| 1. | Anterior part. | SV | Sinus venosus. |
| 2. | Posterior part. | | |
| LAAp | Left auricular appendix. | | |

The right and posterior part of the cavity is somewhat sac-like in form; it communicates with the left extension of the sinus venosus by the aperture previously mentioned, and it receives the four pulmonary veins.

The Ventricles. Right Ventricle. Only the inferior part of this cavity is visible when the ventricular part of the heart is opened from the right side, that is, there is no conus arteriosus or infundibulum. The right auriculo-ventricular valve has only two cusps—the marginal and the septal. The walls are thick, but not so thick as those of the left ventricle, and the cavity opens into the cavity of the left ventricle through a large aperture which occupies the greater part of the situation of the pars membranacea septi. This opening, in the erect posture, lies below and slightly to the left of the aortic orifice (Fig. 3), and from its inferior margin which is adjacent to the right margins of the cusps of the left auriculo-ventricular valve a papillary muscle springs and is connected with the margins of the valve cusps by chordæ tendineæ.

Left Ventricle. The walls of the left ventricle are very thick, and its cavity is separated into two unequal parts by a muscular ridge which commences at one extremity immediately below the interval between the right and left posterior cusps of the aortic valve (Fig. 3), and at that point is continuous with the antero-superior boundary of the opening in the inter-ventricular septum. From this commencement it curves forwards and upwards, and terminates, above, opposite the angle between the anterior and the left posterior cusps of the aortic valve. As a whole, the ridge projects from the very thick upper part of the anterior wall of the left ventricle upwards and to the left into the cavity of the ventricle, and to the right and in front of it there lies a small but distinct segment of the cavity. This segment of the cavity of the left ventricle lies immediately below the right two-thirds of the aortic orifice, the remaining third of that orifice being above the opening in the inter-ventricular septum and the cavity of the larger segment of the left ventricle. We look upon the smaller right segment of the cavity of the left ventricle of this specimen as the representative of the infundibulum, and we

propose to call the ridge which separates it from the remainder of the cavity the infundibulo-ventricular ridge.

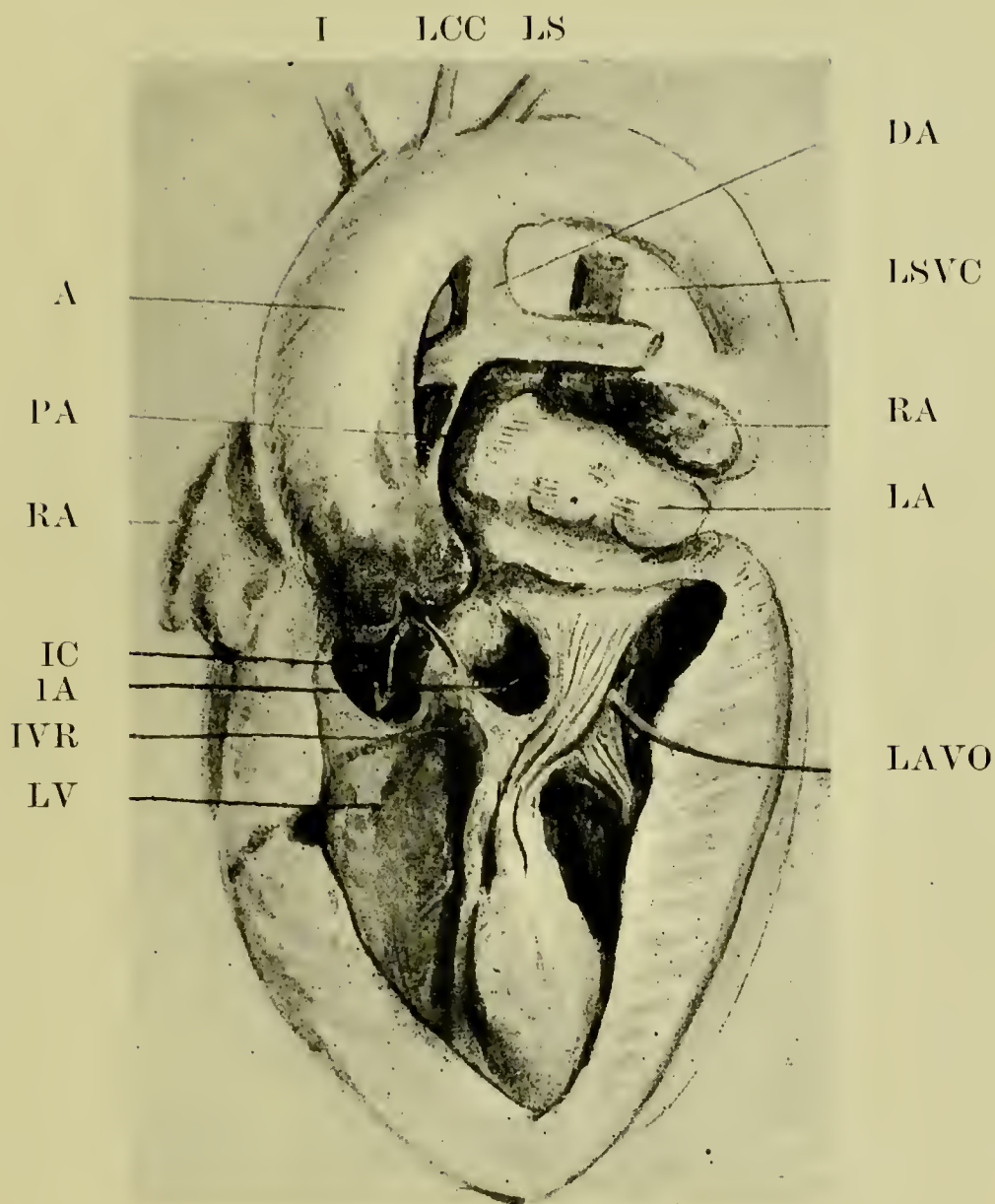
The Pulmonary Arteries. The pulmonary arteries do not communicate with the cavity of either ventricle. The stem of the pulmonary artery is only represented by a fibrous cord which is connected below with the left side of the commencement of the aorta and above with the lower wall of the right pulmonary artery to the right of the ductus arteriosus, therefore in this specimen that portion of the aortic bulb which usually becomes the stem of the pulmonary artery has been transformed into a thin impervious fibrous cord.

The right and the left pulmonary arteries spring from the patent ductus arteriosus through which they received blood from the aortic arch.

The Aorta. The aorta is the only blood-vessel which carried blood from the heart. It springs from the upper right and front angle of the left ventricle, and more particularly from the smaller right segment, and therefore chiefly from the segment which normally should have become the infundibulum of the right ventricle. A portion of the aortic aperture is, however, situated over the cavity of the left ventricle proper; nevertheless, lying mainly over what we believe should have been the infundibular portion of the right ventricle, it is, in our opinion, transposed, and this idea is confirmed by the termination of the fibrous remnant of the stem of the pulmonary artery on the left of the commencement of the aorta.

Remarks on Case II. In this most interesting case, as we interpret it, a left superior vena cava is present following the course of the oblique vein of Marshall and opening into the dilated left extremity of the primitive sinus venosus. The inter-auricular septum is pervious at two separate points. The cavity of the body of the left auricle is separated into two loculi by the pressure of the left superior vena cava on its posterior wall. The infundibular portion of the right ventricle is separated off from that cavity and incorporated with the left ventricle. The inter-ventricular septum is incomplete. There has been a transposition of the aorta and the stem of the pulmonary artery, and the latter has atrophied to a fibrous cord. The blood sent

FIG. 3.



General view of the heart in Case II., showing the obliterated and transposed stem of the pulmonary artery, the patent ductus arteriosus, the right and left pulmonary arteries, and the left superior vena cava. The left ventricle has been freely opened, and shows the interventricular system and its deficiency: the aperture leading to the infundibular cavity, the orifice of the aorta, and the infundibulo-ventricular ridge are also seen.

A	Aorta.	LAVO	Left auriculo-ventricular orifice.
DA	Ductus arteriosus.	LCC	Left common carotid artery.
I	Innominate artery	LS	Left subclavian artery.
IA	Interventricular deficiency.	LSVC	Left superior vena cava.
IC	Infundibular cavity.	LV	Left ventricle.
IVR	Infundibulo-ventricular ridge.	PA	Pulmonary artery (obliterated).
LA	Left auricle.	RA	Right auricle.

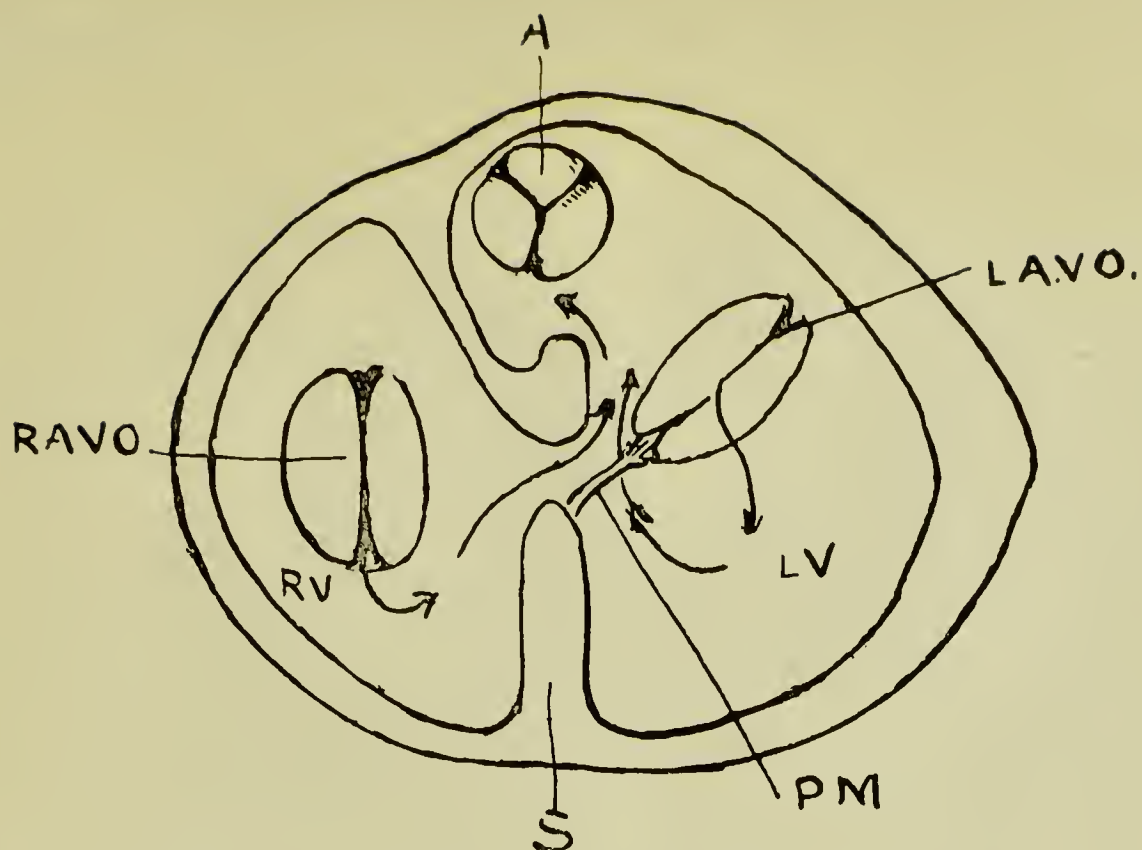


FIG. 4.—Vertical Transverse Section through ventricular part of heart of Case II (diagrammatic). Seen from the front.

A Aorta.	S Septum.
LAVO Left auriculo-ventricular aperture.	RAVO Right auriculo-ventricular aperture.
LV Left ventricle.	RV Right ventricle.
PM Papillary muscle.	

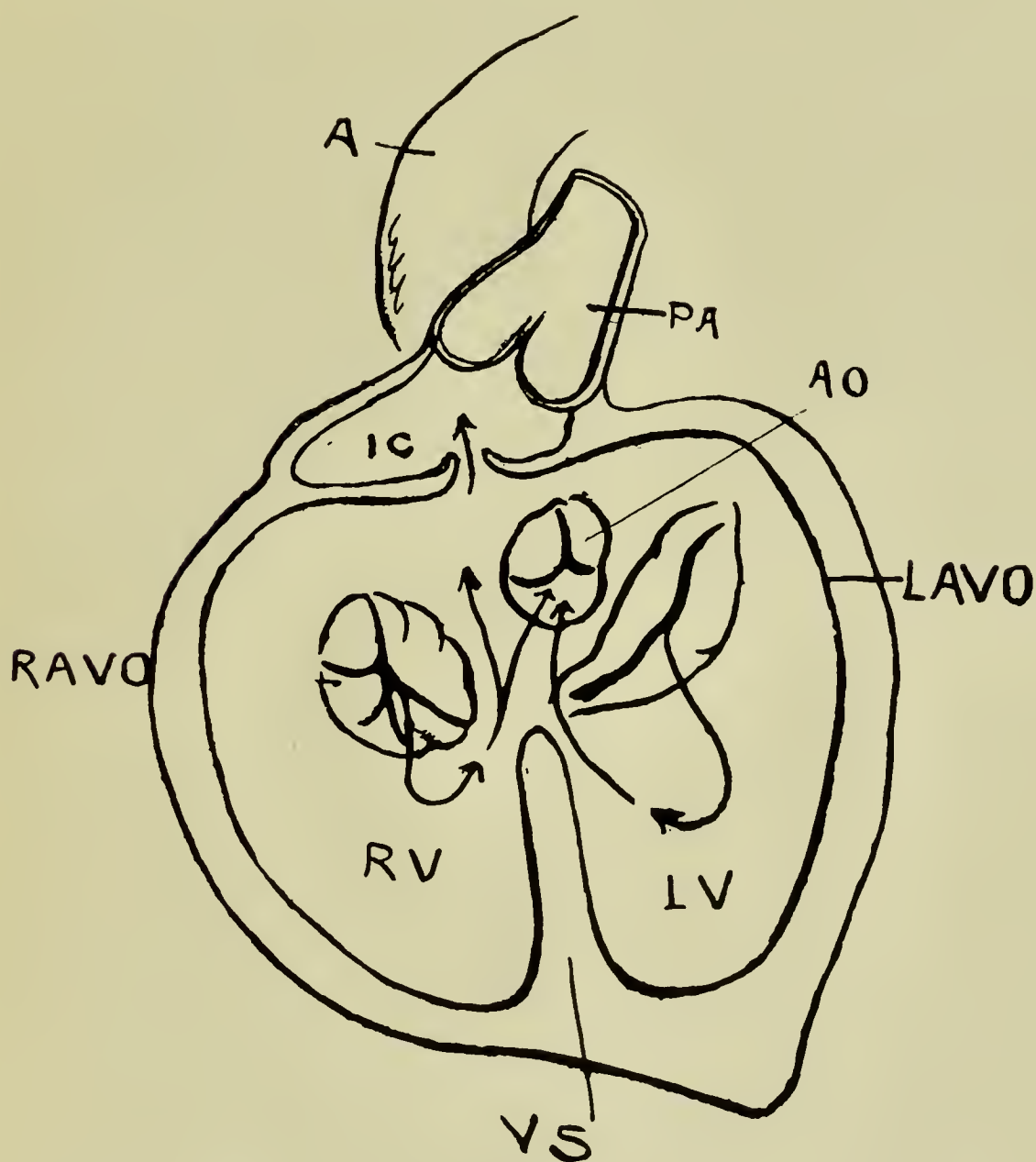


FIG. 5.—Diagrammatic view of the Ventricles of Case III.

A Aorta.	RAVO Right auriculo-ventricular orifice.
AO Aortic orifice.	RV Right ventricle.
IC Infundibular cavity.	VS Interventricular septum.
LAVO Left auriculo-ventricular orifice.	
LV Left ventricle.	

to the lungs during life must have passed from the left ventricle by the aorta and thence through the pervious ductus arteriosus from which the right and left pulmonary arteries arise. The dorsal part of the left fifth aortic arch, which usually atrophies, has remained widely open, and forms the channel of communication with the right and left pulmonary arteries into which the ventral part of the fifth left arch and adjacent parts of the apex of the aortic bulb and the fifth right arch have been incorporated, whilst the segment of the aortic bulb which should have become the stem of the pulmonary artery has been obliterated.

During life blood was carried to the right auricle most probably by an inferior vena cava and a left superior vena cava, the latter being the persistent left duct of Cuvier. From the right auricle the major part of the blood passed into the right ventricle and the minor part through the inter-auricular foramina into the left auricle. From the right ventricle the blood was projected through the inter-ventricular foramen into the left ventricle, meeting, on its entrance, with the blood of that cavity together with which it passed into the aorta, the blood of the left ventricle being mainly oxygenated blood returned to the left auricle from the lungs, but with a slight admixture of venous blood which traversed the inter-auricular foramina. The blood in the aorta, therefore, was mixed blood, some of which was distributed to the head and neck, some to the body and limbs, and some passed by the ductus arteriosus into the right and left pulmonary arteries and thence to the lungs and left auricle.

CASE III. Communication between the right and left ventricles through an inter-ventricular foramen. The infundibulum almost entirely separated from the ventricles.

We are indebted for this specimen to Dr. Emanuel, of Birmingham. It was taken from a boy aged 7 years, whose fingers and toes were clubbed, and who died with signs of cardiac failure and general anasarca after exhibiting marked cyanosis during life. The heart had undergone general hypertrophy, but the hypertrophy was most marked in the region of the right ventricle.

The Auricles. The auricles communicated with each other by a well-marked inter-auricular foramen situated at the upper and anterior part of the fossa ovalis. On the left side this aperture was situated between two small but distinct muscular bands. In all other respects the auricles were quite normal.

The Ventricles. The ventricles are greatly enlarged, both as regards the size of their cavities and the thickness of their walls; this excentric hypertrophy is noticeably more marked in the right than in the left ventricle.

Right Ventricle. The right auriculo-ventricular orifice is guarded by five cusps instead of the usual three; three of the five are subdivisions of the right or marginal cusp, and they receive chordæ tendineæ from the muscoli papillares of the inferior and septal walls. The moderator band is short and very thick. To the left of the infundibular cusp of the right auriculo-ventricular aperture there is a large opening in the upper part of the inter-ventricular septum, in the situation usually occupied by the anterior part of the pars membranacea septi, and immediately above this inter-ventricular opening is the orifice of the aorta which lies partly over the right and partly over the left ventricle. Above and in front of the inter-ventricular foramen, and separated from it by a prominent muscular band, is a small aperture which forms the only means of communication between the body of the right ventricle and the remains of the infundibulum. The margin of the aperture is formed by a firm and, in the hardened specimen, inextensile fibrous band; in the outer periphery of this band numerous chordæ tendineæ are attached which are connected with columnæ carneæ on the anterior wall of the ventricle. The infundibulum is a relatively small somewhat conical-shaped cavity, possessing an anterior and a posterior, a right and a left lateral wall. The anterior and posterior walls meet below, forming a narrow sulcus. In the floor of this sulcus, near its anterior and left extremity is the small aperture of communication with the body of the right ventricle. The opening of the pulmonary artery is in the left lateral wall of the infundibulum, two of the cusps of the pulmonary valve being in front and one behind. The walls of the infundibulum are muscular but relatively thin.

Left Ventricle. Although the left ventricle is hypertrophied it is relatively small as contrasted with the right ventricle. Its cavity communicates with the auricle in the usual way, and the mitral valve is normal. The right and anterior part of its cavity is more dilated than usual, and it communicates with the right ventricle through the inter-ventricular foramen, and the aortic orifice is situated at its upper end.

The Pulmonary Arteries. The stem of the pulmonary artery springs from the left of the small and almost isolated infundibular cavity. It is of considerable size, but its walls are thin; it divides in the usual way into right and left branches, and neither the stem nor its branches have any communication with the aorta, for the ductus arteriosus is completely obliterated. The pulmonary valve consists of three cusps, two of which are placed anteriorly and one posteriorly.

The Aorta. The aorta springs partly from both ventricles, its orifice being situated over the inter-ventricular foramen, but more to the left than to the right of the margin of that orifice. The two cusps of the aortic valve are placed one anteriorly and the other posteriorly. The arch of the aorta and part of the descending thoracic aorta are still attached to the specimen. In the arch the position of the opening of the ductus arteriosus is marked by a small cicatrix, and an examination of the descending aorta shows that neither the bronchial nor the aortic inter-costal arteries are larger than usual, from which it may be inferred that no extra amount of blood passed to the lungs through these channels.

The Veins. The venæ cavæ and the pulmonary veins are normal in number, size and appearance.

The Circulation. The circulation must have been carried on in much the usual way, except that a part of the blood from the right ventricle passed directly into the aorta.

It is difficult to understand, from an examination of the hardened specimen, how the amount of blood necessary for the pulmonary circulation, as indicated by the size of the pulmonary artery and pulmonary veins, could have passed through the small and apparently undilatable orifice by which the right

ventricle communicated with the infundibulum. It is possible that during life the margin of the orifice was more extensile than now, and this possibility appears to receive support from the connection of the columnæ carneæ with the periphery of the fibrous ring by which the orifice is bounded.

CASE IV. Cavities of the right and left ventricles continuous. Inter-ventricular septum practically absent. Infundibular chamber very largely separated from the remainder of the ventricular cavity by a well-formed infundibulo-ventricular septum. Transposition of the aorta and pulmonary artery.

For this specimen also we are indebted to the kindness of Dr. Emanuel; it was taken from the body of a male child, aged twenty months in whom during life the only trace of cyanosis was a slight blueness of the lips. There was no clubbing of the fingers, but for some weeks before death, which was due to septic thrombosis of the pulmonary artery following pleurisy, there had been attacks of sudden exhaustion.

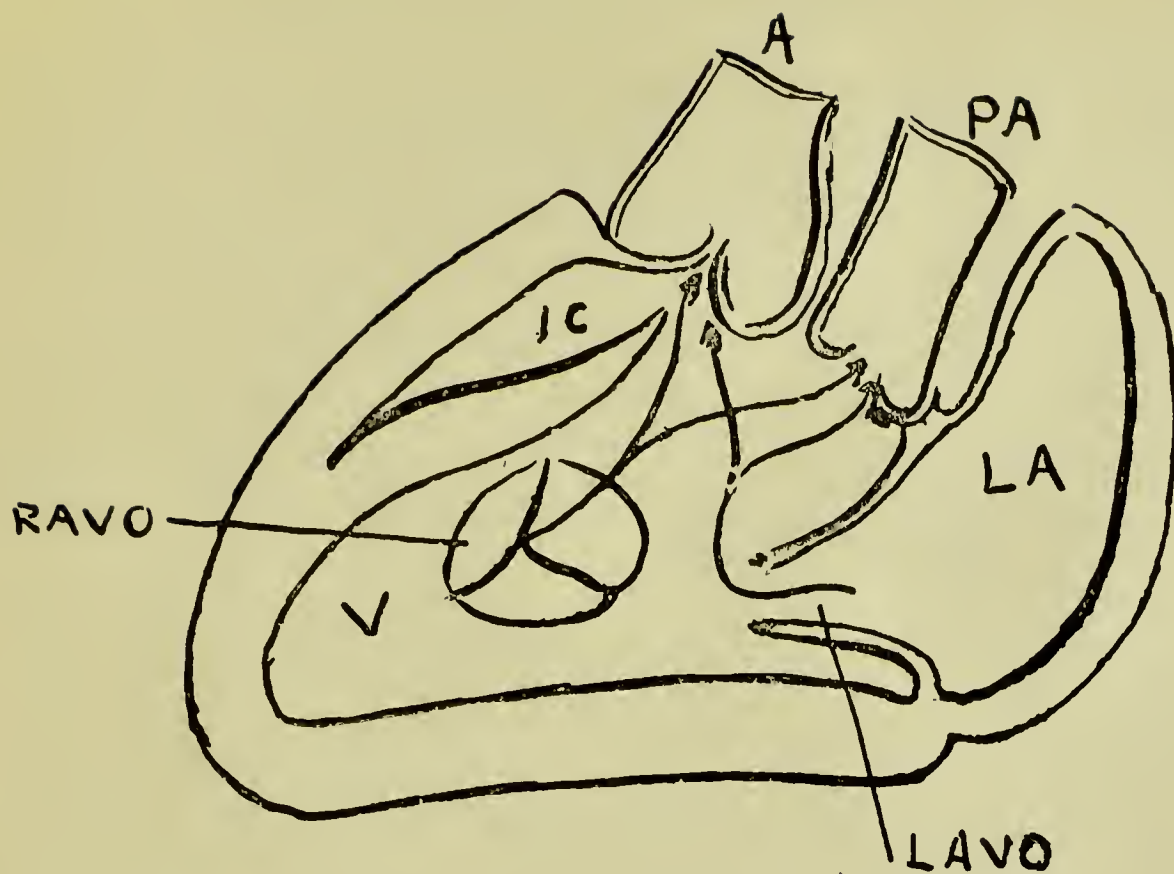
The heart is of about the usual size at this age, and except that the aorta and pulmonary artery appear to be transposed and that there are no inter-ventricular sulci its external appearance is normal.

The Auricles. In connection with these chambers nothing particular is noticeable except that the foramen ovale is completely closed and that the left auricle receives only one pulmonary vein on each side.

There are two chambers in the ventricular part of the heart—a large chamber which occupies the greater part of the interior and a much smaller space which occupies the position of the infundibulum of the normal heart. These two cavities communicate through a wide aperture situated at the upper part of the intervening septum and immediately below the posterior cusp of the aortic valve.

The smaller cavity, at its lower extremity, is a more or less cleft-like space which is situated just above the middle of the length of the ventricle, but it widens out above, and occupies an area equal to about two-thirds of that of the orifice of the aorta with which it is in direct continuity.

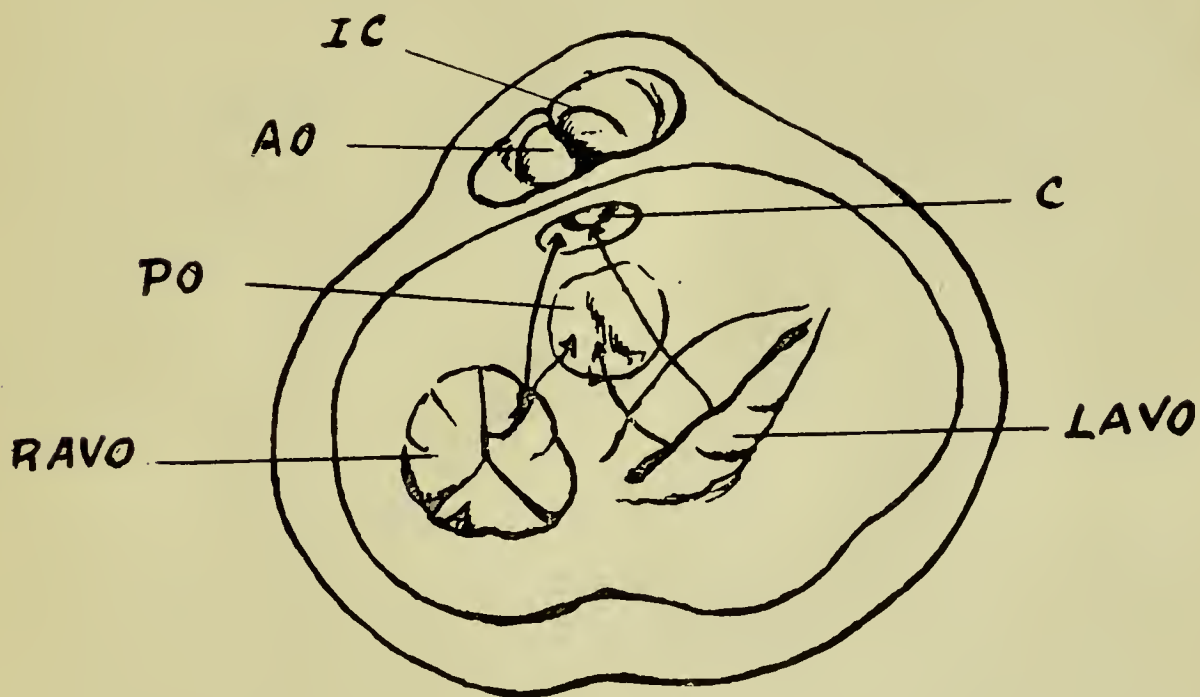
FIG. 6.



Sagittal section of the heart of Case IV. (diagrammatic).

- | | |
|---|--|
| A Aorta. | PA Pulmonary artery. |
| IC Infundibular cavity. | RAVO Right auriculo-ventricular orifice. |
| LA Left auricle. | V Ventricle. |
| LAVO Left auriculo-ventricular orifice. | |

FIG. 7.



Transverse section of the ventricular part of the Heart in Case IV. (diagrammatic.) Seen from the front.

- | |
|--|
| AO Aortic orifice. |
| C Communication between infundibular cavity and ventricle. |
| IC Infundibular cavity. |
| LAOV Left auriculo-ventricular orifice. |
| PO Pulmonary orifice. |
| RAOV Right auriculo-ventricular orifice. |

The aortic orifice is guarded by three semi-lunar cusps of which two are placed anteriorly and one posteriorly, and the coronary arteries spring from the sinuses of Valsalva in association with the anterior cusps.

Remarks on Case IV. This case is practically, so far as the ventricular part of the heart is concerned, a more advanced stage of the same condition as that met with in Case i. It differs from it in the fact that the septum between the larger and smaller segments of the ventricular chamber is more complete and the aorta rises more definitely from the smaller chamber. So far as the circulation was concerned it is obvious that the venous and oxygenated blood were mixed in the larger ventricular cavity, and that the mixed blood was forced thence partly through the aperture between the two ventricular chambers into the aorta and partly into the pulmonary artery. Moreover it is obvious that the same ventricular force had freer play on the pulmonary than on the aortic orifice, therefore the pulmonary blood-pressure must at least have been equal to the systemic unless it was reduced by the contraction of the pulmonary orifice.

GENERAL REMARKS.

We have grouped these cases together because in all the infundibular portion of the ventricular chamber tends to be separated to a greater or less extent from the other portions of the ventricular cavity. In Case iii. it communicates only with the right ventricle, but the latter communicates also with the left ventricle. In Case ii. it constitutes a small segment of the left ventricle, and is only defined from the latter by a muscular ridge. In Cases i. and iv. the greater part of the cavity of the right ventricle is blended with the cavity of the left ventricle, the normal inter-ventricular septum not being developed and the infundibular part of the right ventricle forms a distinct chamber which communicates with the larger cavity, but opens more directly into the aorta which in both cases occupies the position usually taken by the pulmonary artery.

The number of cases is not sufficient to form a basis for any definite opinions, but the occurrence of transposition of the aorta

and pulmonary artery in three cases in which the infundibular part of the heart is more closely associated with the left than with the right ventricle is suggestive.

It is interesting also to note that although the hearts deviated so far from the normal condition still the abnormal condition was not in itself fatal, though no doubt in the last three cases it led to the death of the patient.

NOTES ON SOME OF THE LESS FAMILIAR JOINT AFFECTIONS.

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IN a former paper (*Medical Chronicle*, July, 1906) the writer made suggestions as to the names and methods of grouping of Diseases of the Joints. In the present article it is proposed to give examples of a few forms of arthritis selected from among those which are perhaps most commonly misunderstood and wrongly named, and worse still, but consequently, wrongly treated. The errors are believed to be due in part to the habit of calling many different diseases Rheumatic or Rheumatoid without due investigation, and though it would be useful to enter into this subject in detail it is so intricate that its discussion has had to be postponed, and it is only proposed to relate examples of a few of the many forms of arthritis which have been, or are likely to be, thus misunderstood. In doing so no attempt is made at any thing more than illustration of those particular features which are likely to lead to misinterpretation. No complete description or record could be attempted, and the notes are meant to be merely suggestive of certain lines of enquiry which may usefully be pursued in doubtful cases of Arthritis.

An examination of some of the old specimens in any Pathological museum will show more or less good examples of distortion of the head of the femur and other bones with "eburnation," osteophytic outgrowths around the edges of the articulation and more or less formation of new bone, either encrusting the adjoining area or developing in stalactite fashion in the attachments of neighbouring muscles and fibrous structures. Unfortunately these specimens have no clinical history and are simply labelled "Rheumatoid Arthritis" or some similar name.

That some of these conditions are the result of injury in the form of a single hurt of severe degree or of repeated slight strains or of constant overuse in certain occupations is the view

most strongly championed and most carefully worked out by Arbuthnot Lane. But though he refers to the occupations which produce certain of these lesions, we are not supplied with sufficient proof in the shape of clinical histories to make the evidence satisfying. On the other hand certain other lesions are found either in association with the more purely articular changes in the limbs or in the form of abnormal conditions of the spinal column, which are less credibly attributed also to the effects of labour. That a single severe injury may produce some of such conditions can hardly be disputed, and figs. (1) and (1A) show such changes in the shoulder joint, probably as the result of the fracture of the greater tuberosity of the humerus. Though the connection is less obvious, we may admit that the osseous growth in the structures not immediately adjoining the articulation may also be traumatic, as such view is supported by analogous conditions found under other circumstances. It seems to be well-established and is indeed familiar knowledge, that some of these lesions are traumatic, but it is much more doubtful whether Mr. Lane's view, that all the "Rheumatoid" and some of the other similar lesions are the result of injury, is a satisfactory one. If we examine specimens such as figs. ii.—viii. of the condition known as "Spondylitis deformans," and classed as one of the "Rheumatoid" changes, on the one hand, and as a traumatic condition on the other, it is difficult to believe that the bony deposit and the changes in the vertebræ are simply the result of injury, either on an isolated occasion or frequently repeated. The bony deposit, which has been well likened to a "guttering candle," does not suggest the conditions found elsewhere as the result of injury, but rather an ossification in a bulky soft effusion which has been rather rapidly poured out, and like a flow of lava has run down the spine and set or ossified as it descended.

Dr. Goldthwait (*Boston Med. and Surg. Jour.*, vols. CXLI. 1899 and CXLVI. 1902) has figured and described some good specimens, and gives photographs of patients said to be suffering from this condition, but we have no demonstration that the living patients had spines like those figured, nor have we any satisfactory account of the causation of the condition.



Fig 1.—Upper end of humerus. The greater part of the head of the bone is missing. There is an old fracture of the greater tuberosity. The portion of head left shows eburnation and the effects of attrition.



Fig 1A.—Upper end of humerus. There is an old fracture of the greater tuberosity. There is some alteration in the form of the head with deposit of new bone.

The link between the old museum specimens and the living patients whose history can be obtained is missing, and this discovery of the complete history with verification of the condition post-mortem would be a very valuable addition to our knowledge. Dr. Goldthwait does not record the result of X-ray examination of the spine in his cases. In one case of my own with symptoms closely resembling those of some of his patients, a skiagram did apparently show such bony changes together with atrophy of the bodies. An important, though, so far as I know, isolated, observation is that of Dr. MacCrae, that in a case of typhoid spine a radiogram showed bony thickening. On the other hand, C. J. Wilson quotes two cases in which radiograms were taken. In one nothing abnormal and in the other only weakening of the shadow was found.

Examination of specimens of Spondylitis suggest that the pathology of all cases is not the same, and it is certainly not improbable that in at least some instances the condition is due to one of the forms of systemic (bacterial or autotoxic) arthritis. Dr. Goldthwait mentions gonorrhœa, injury, cold, and various debilitating conditions, but does not dogmatise on the subject.

While writing the present notes, the kindness of my colleague, Dr. Wilkinson, has enabled me to see a case exactly in point. An ex-soldier, who had a history of a venereal sore and gonorrhœa, and who showed the scars of old buboes, was admitted to the Infirmary in December, 1907. Since leaving the army he had worked laboriously and in wet and cold, and had taken a great quantity of alcohol. For twelve months he had noticed a gradually increasing stiffness of his back, more especially in the cervical region and loins, with pain and disability. None of the joints of the limbs were affected, though there was aching pain in the thighs and upper arms, nor was the jaw stiff. On examination the man was sallow and looked ill. The whole spine was nearly absolutely rigid, except that the power of flexion of the head upon the atlas seemed free. Some thickening about the cervical spine appeared to be present on lateral palpation, and the region of the left sacro-iliac joint was swollen. The liver was enormously and smoothly enlarged. There was evidence of marked arterial degeneration. There

was no ascites. An X-ray photograph, taken in an antero-posterior direction (Fig. ii. B) showed blurring of the outlines of the vertebræ, but a lateral view (Fig. ii. A) clearly displayed rounded smooth bosses on the anterior aspect of the vertebral bodies exactly like those in the figures. This appears to be a clear case of the condition described as spondylitis deformans, and, with the exception of the one already mentioned, is the first example I have seen of such a condition being illustrated by an X-ray photograph taken during life. The etiology of the disease is doubtful since many possible causes were present. Gonorrhœa, alcohol, exposure to wet and cold, ague and "low fever" in the West Indies, and perhaps syphilis, all figured in his previous medical history.

This man had no marked nervous affection. There was slight muscular wasting, and a certain amount of lateral curvature of the spine, with a tender spot at the level of the 6th cervical vertebra, but no evidence of tuberculous disease.

On the whole, it is probable that this condition, like many of the other forms of joint lesion labelled "rheumatoid," is either bacterial or autotoxic in origin.

Under the heading of acute local traumatic arthritis must at present be put perhaps that variety associated with hæmophilia, and as the subject is an interesting one some experience in regard to it may be mentioned here.

Hæmophilic arthritis or arthritis following upon an injury to a joint in a young person the subject of hæmophilia is, at its first occurrence, not more likely probably to produce any permanent joint lesion than is a hæmarthrosis in any other patient. It is rather the repeated hæmorrhages which produce the permanent changes found in a bleeder's joints. The condition, though of course not common, is not so rare as to be negligible, and it is so exceedingly likely to be overlooked, or rather mistaken for some other disease, that it is quite worth bearing in mind in any obscure or doubtful joint affection that may be met with. I have come across probably something like a dozen cases, and have notes or recollections of seven. It is of course highly probable that any bleeder will get, some time or other, an injury that will produce hæmarthrosis, and if this is

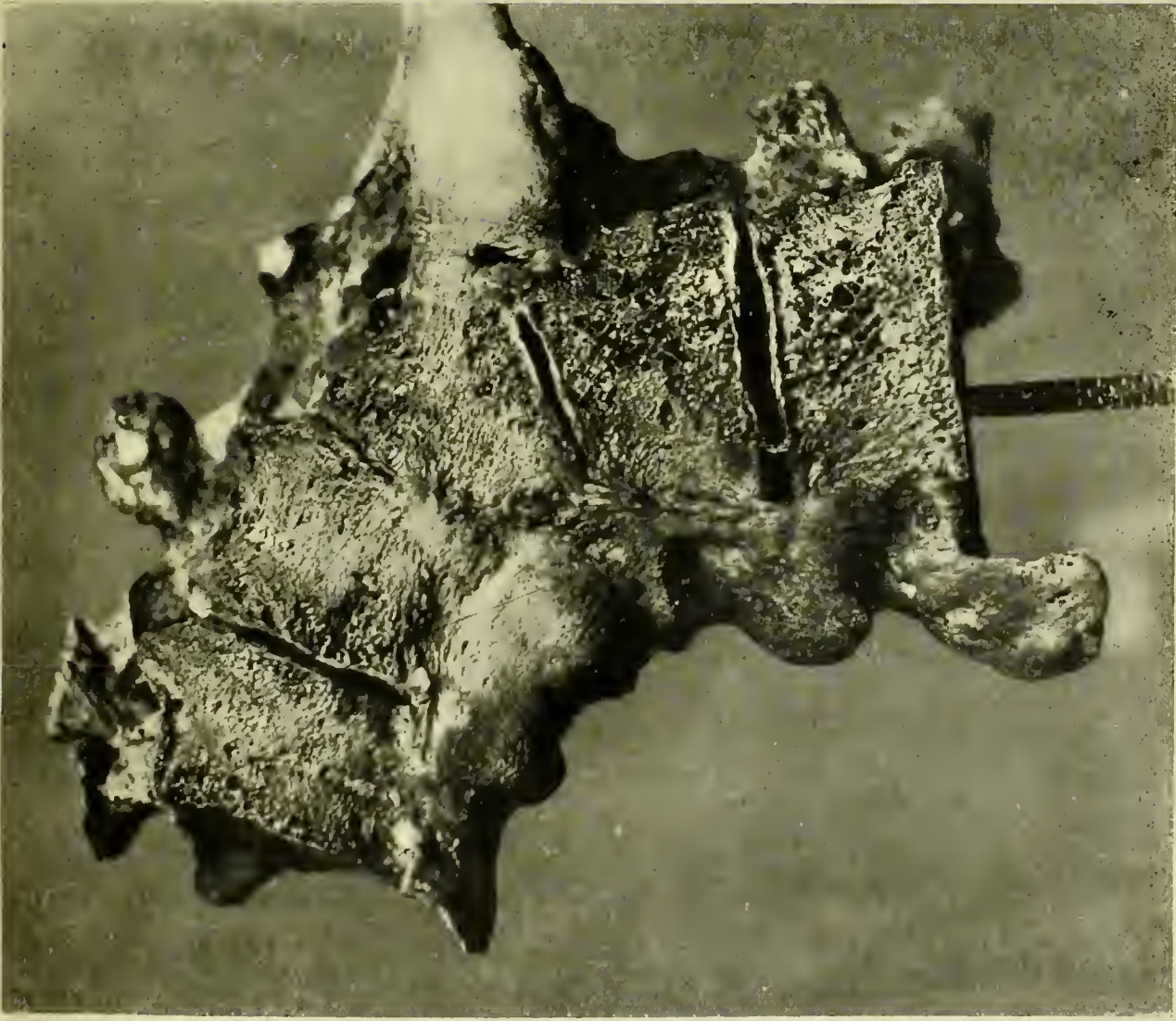


Fig. 2.—“Spondylitis deformans.” The lava-like or guttering deposit of new bone cementing together the bodies is well seen. There is a marked lateral curvature.



Fig 2A.—Spondylitis deformans (lateral view) shows rounded bosses of new bone on the front of the vertebral bodies.



Fig 2B.—Spondylitis deformans showing bony deposit on the face of the cervical vertebræ.—Cf. Fig. 8.

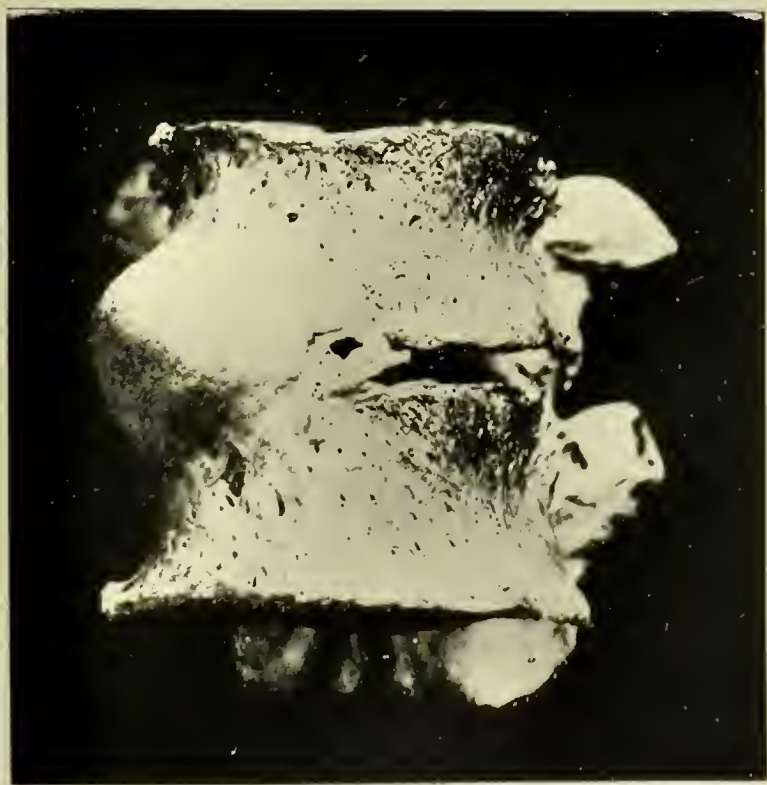


Fig. 3.—An isolated boss of new bone sealing together two vertebral bodies.

repeated certain definite changes in the joint are liable to be set up.

One of my earlier cases was that of one of two brothers, who were both markedly hæmophilic, though there did not appear to be any corresponding family history. When I first saw the boy he was 14 years old, and had sprained his left knee nine months before; at that time the joint filled with fluid and gave trouble off and on until I saw him. The joint was enormously distended with blood, and was in the condition of an acute hæmarthrosis. Twelve months later the boy was seen again. He was pale, and the joint was very painful. There was thickening, crackling and occasional slipping of the joint exactly like the condition found in certain joints labelled "rheumatoid arthritis." There was some slight shortening of the limb, perhaps due to interference with growth by the joint trouble. At the time of my first inspection the brother had an ankle joint half full of blood with discolouration like bruises around the part. I saw the knee again after another interval of a year, and found much deformity together with swelling. He had had a fall six weeks prior to my visit, and was then getting better. My notes say that eleven years later the joint was much deformed and crippled, and the seat of repeated attacks of an acute or subacute character, with pain and disability. He had had hæmorrhage into one elbow some three years before my last note.

In a man of 42, whom I saw in 1894, there was a family and personal history of bleeding. The left knee was well till twelve years before my inspection, when he injured it by a blow; pain lasted for a few days, but he did not rest it. Some twelve months later he had pain in the left hip "after sleeping in a damp bed." The knee never quite recovered, and recently had become worse; it was weak and painful, especially after he had been standing, and he had a feeling as of the joint giving way. He could not walk twenty yards. The other knee, one great toe and both elbows were in a corresponding condition.

Another instance was that of a child of $3\frac{1}{2}$ years, whom I saw in April, 1901. There was a story of various bleedings since the age of three months. "The slightest blow always raises a bruise," I was told. In October, 1900, the knee was

injured, and became swollen, and the swelling never quite subsided, though he was able to run about. On subsequent occasions, without any known injury, pain and swelling returned. When I examined him the joint was again full of fluid, but there did not seem to be any serious restriction of its use except during an attack.

Recently the following case has been under my notice :—

In June, 1907, a boy of 11 years (Terence C.) was sent into my wards suffering from a swollen and painful knee. At the first examination of the joint, though the appearance rather suggested tuberculosis, the mode of onset and one or two other features led to a careful enquiry in regard to hæmophilia. The boy's mother was alive and well. His father was alive, but suffered from periodic bleeding from the nose which was difficult to check. An elder brother died in youth from hæmorrhage after extraction of a tooth. Two sisters were alive and well. Since he was 5 years old the boy had had periodic attacks of swelling and pain in his knee occurring about twice a year. Each attack lasted about a fortnight. In the intervals he could run about and play football. On one occasion epistaxis and on another bleeding from a pimple lasted for a considerable time. No other joint had been affected. On this occasion pain and swelling came on suddenly, and on admission the joint was semi-flexed, though mobile through a fairly full range. There was slight thickening of the articular surfaces of the femur and tibia. Some muscular wasting was noticed. He improved rapidly under treatment, and was sent to the Convalescent Hospital on July 3rd. Early in September he was re-admitted with another attack. The joint was full of blood, and an X-ray photograph showed some irregularity in the outlines of both femur and tibia. The fact that in this instance the tendency was transmitted through the father's side is noteworthy.

It is important to bear in mind that tubercle occurs in bleeders, and in one instance I unwittingly erased a knee joint in such a boy. Happily he was not a severe case of hæmophilia, and recovered, though we had trouble with him. He also had caries of the spine with psoas abscess. In another lad whom I had opportunities of seeing occasionally a knee joint was affected,

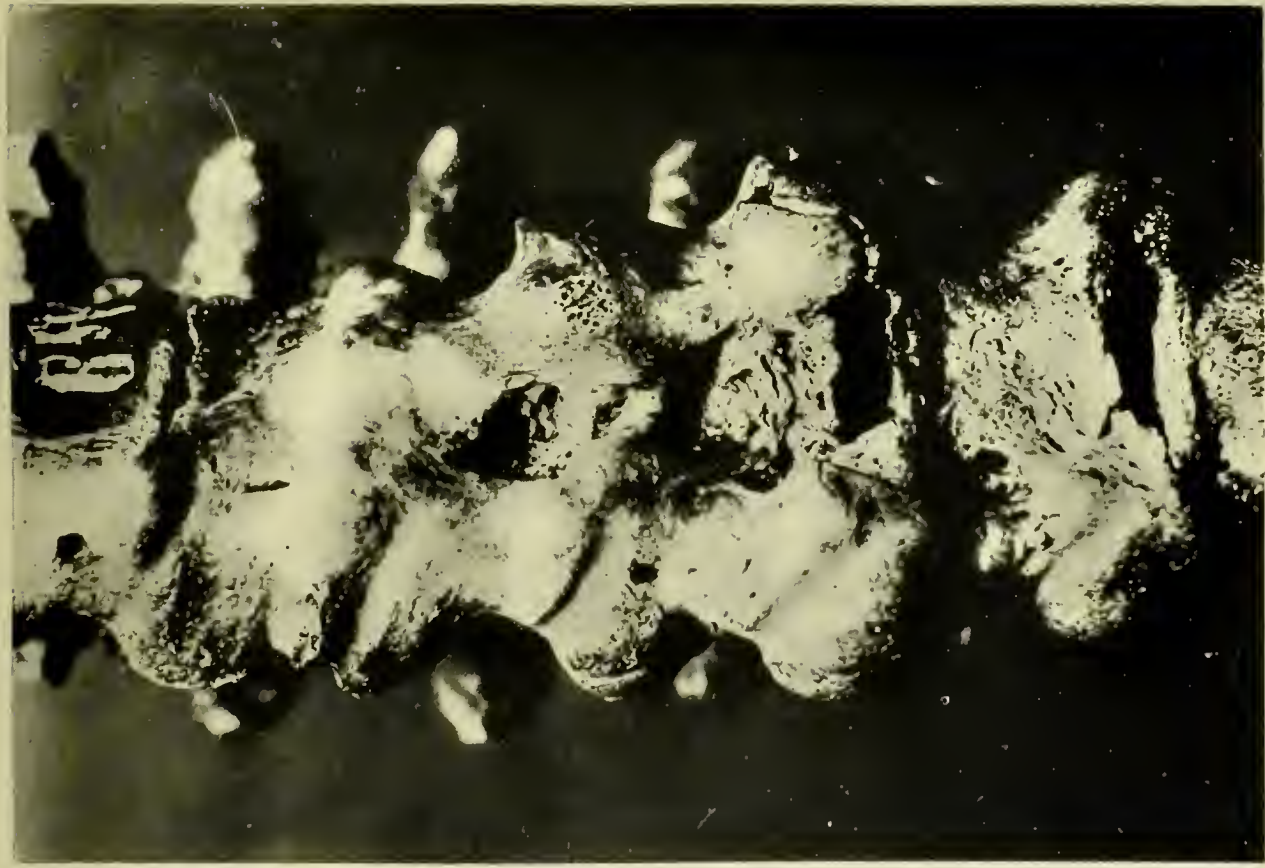


Fig. 4.—“Spondylitis deformans.”



Fig. 5.—“Spondylitis deformans.”



Fig. 6.—“Spondylitis deformans.” The bony deposit is less bulky than it is in some of the other specimens. There is a certain amount of antero-posterior curvature.

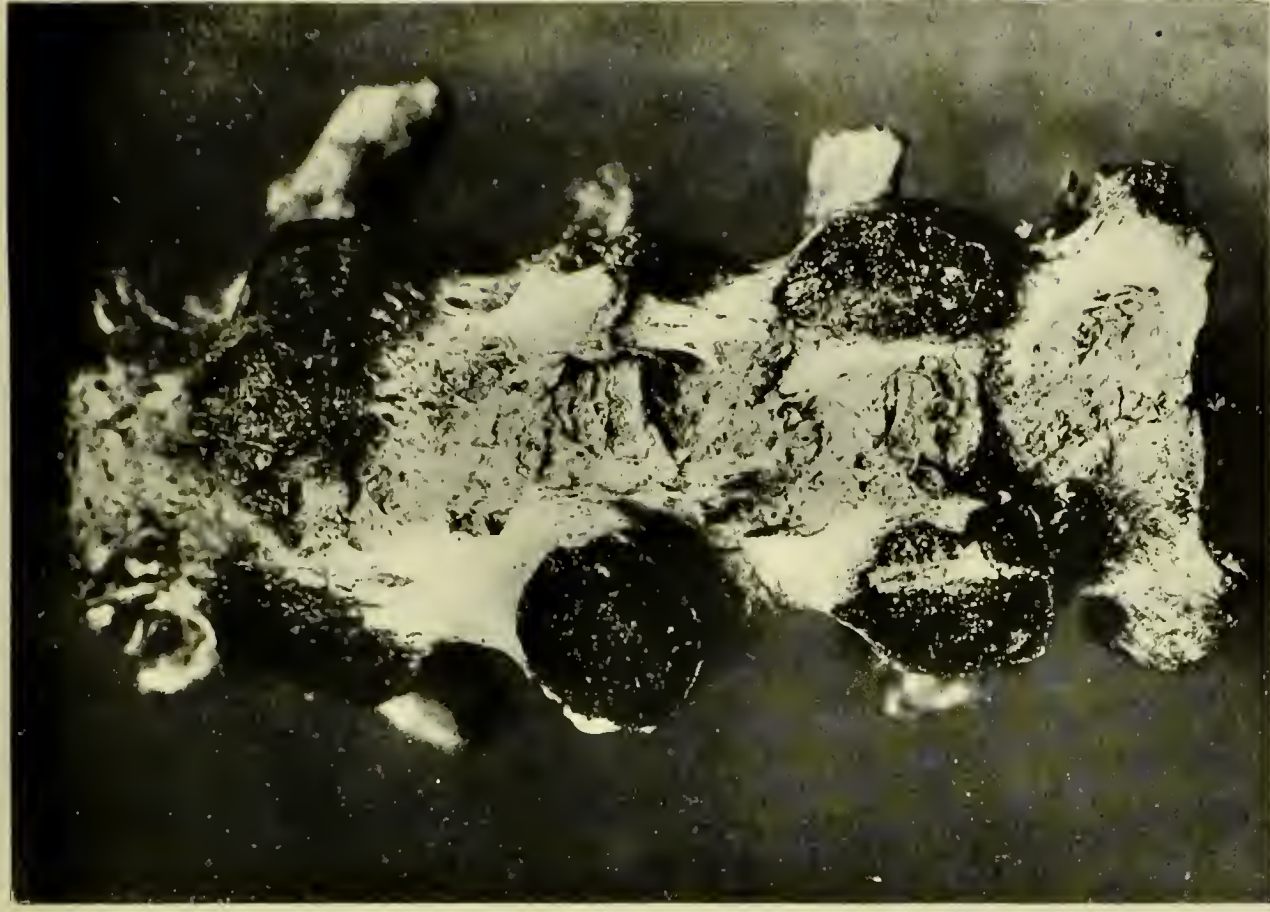


Fig. 7.—“Spondylitis deformans.” The surface of some of the bosses is broken off, and the cancellous structure of the new bone is displayed.

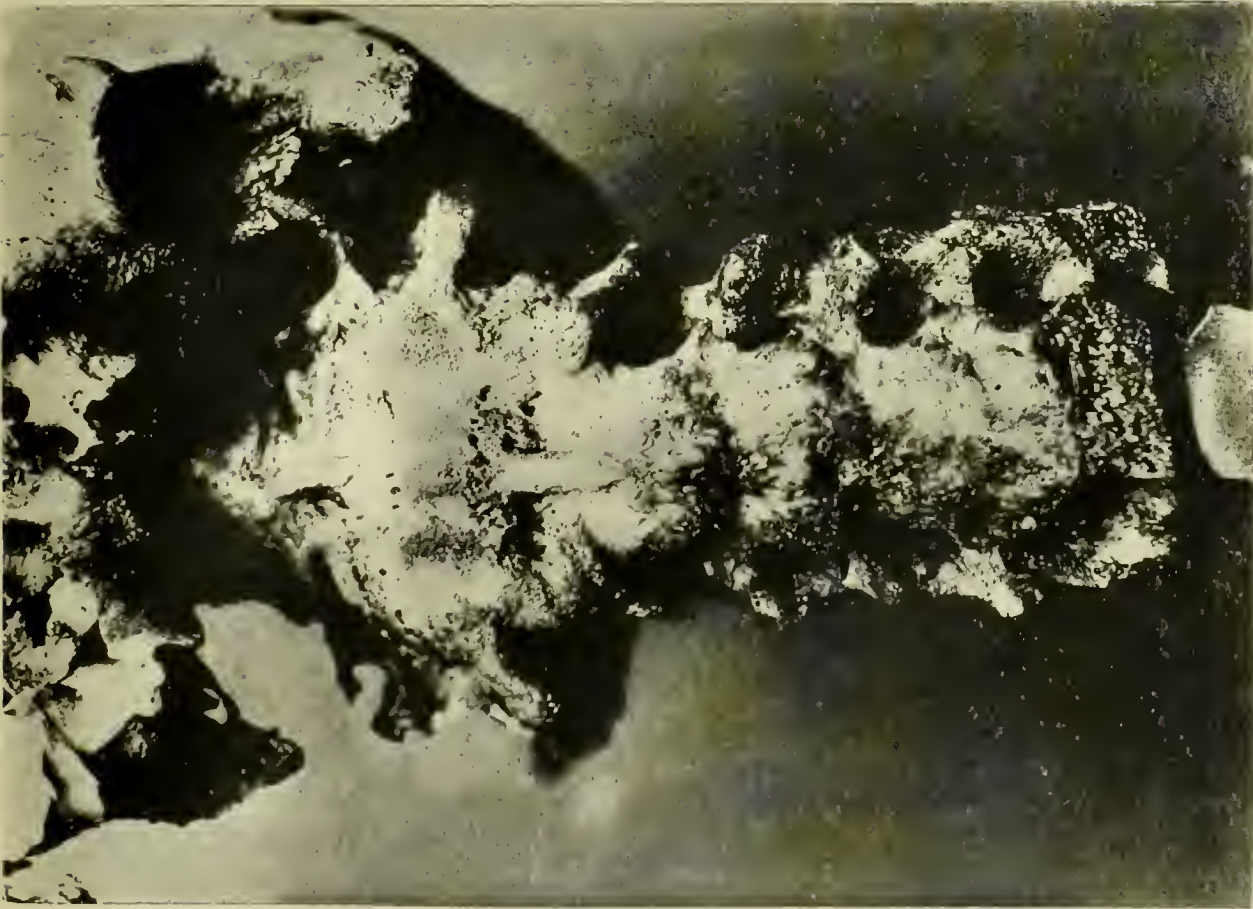


Fig. 8.—Spondylitis deformans of the cervical spine. The bony deposit is more diffuse than in some of the other specimens, and extends upwards to the skull.—Cf. Fig. 2B.

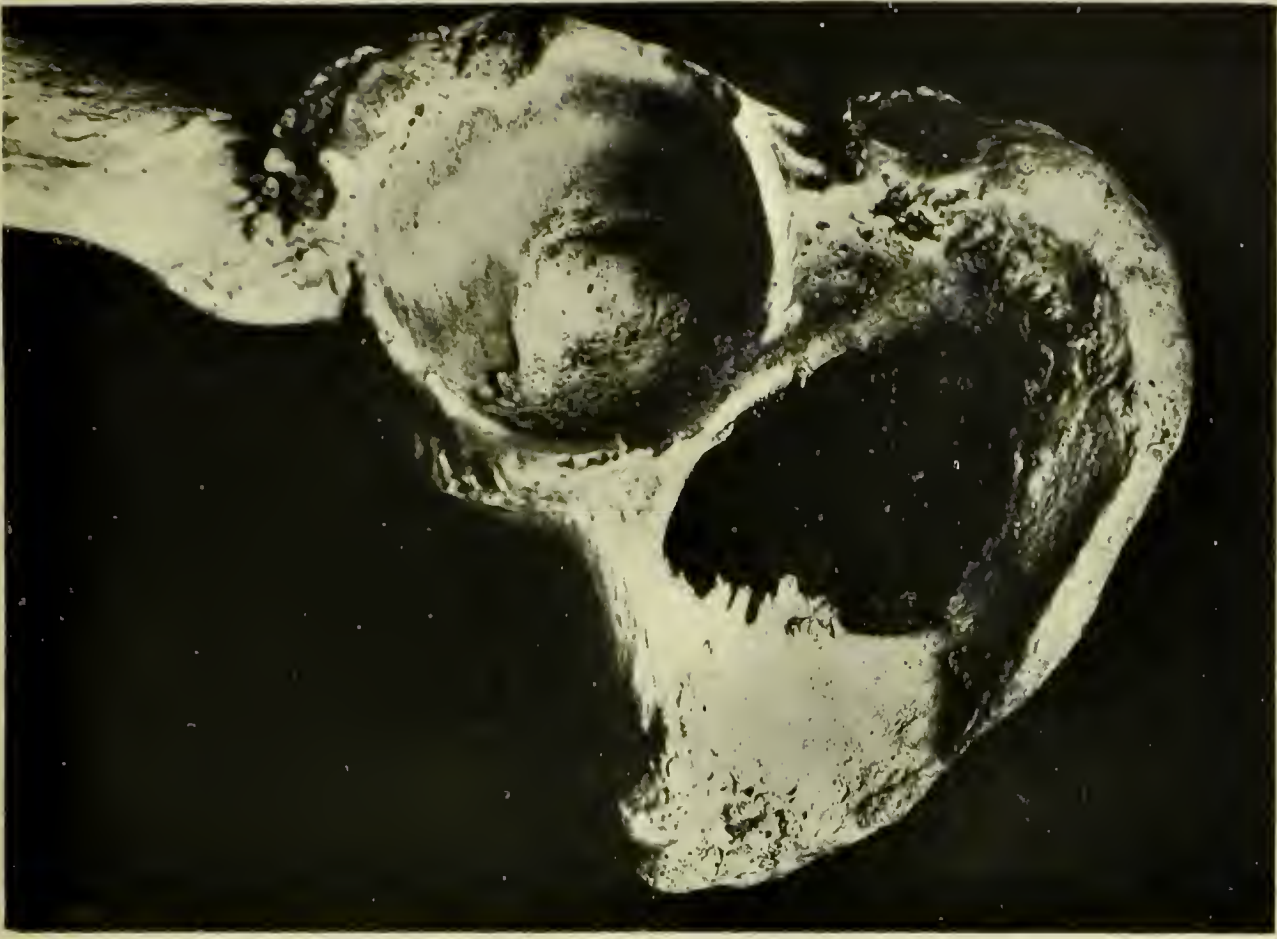


Fig. 9.—The acetabulum is altered in shape and surrounded by new bone. Stalactitic formation of bone has taken place around the obturator foramen and about the attachment of the hamstrings, etc.



Fig. 10.—Eburnation and attrition changes are well marked, with some new-bone formation.



Fig. 11.—An extreme degree of change in the head of the femur, with bony deposit around the upper end of the shaft.

and he had, on one occasion at least, suffered from such severe hæmoptysis that he was almost moribund, and I was told that one lung was probably extensively injured by tubercle, though it is no doubt questionable how far the mischief may have been the direct effect of the hæmorrhage into the lung. Since the above was written he has died of exhaustion from long-continued epistaxis. It has been stated (Koenig) and denied (Froelich) that acute hæmophilic arthritis leads to chronic articular deformity. There is not the slightest doubt that it does so, and that the resulting condition closely resembles clinically the changes in so-called rheumatoid joints. This fact is an illustration of the importance of bearing in mind hæmarthrosis as a possible starting point of some of the lesions labelled "rheumatoid."

Marsh describes the wearing away of the cartilages with granular and fibroid degeneration and fissuring or loosening from the bone. At the same time, there may occur, he tells us, proliferation of the cartilage cells, which may escape into the cavity. These changes with weak ligaments, thickened synovial membranes and nodular excrescences from the bones are of course identical with the changes found in some forms of so-called "rheumatoid arthritis."

An interesting illustration of the effect of repeated traumatism is seen in cases operated upon for displaced semilunar cartilage of the knee or other loose body. If the attacks have been often repeated and the trouble is of long duration the secondary changes in the joint consist in thickening of the fringes, degeneration of articular cartilage and so on. Similar changes are seen in hallux valgus and in the joints of other toes similarly distorted by the pressure of ill-shaped boots, and such articulations afford striking examples of advanced "rheumatoid arthritis."

A single severe sprain of an inter-phalangeal joint will often give rise to precisely the conditions described as the "fusiform variety" of rheumatoid arthritis.

Pneumococcic arthritis is probably one of the commonest forms of suppurative arthritis, though we can only come to this conclusion as yet by comparing the clinical features of the

instances in which the presence of the pneumococcus has been proved with those in which no investigation has been made. Thus scientific proof is wanting, but clinical evidence justifies us in believing that many of the cases of so-called "spontaneous" or "idiopathic" suppurative arthritis, and probably many of the acute epiphysary lesions are due to the pneumococcus. It is therefore likely that it is commoner in children than it would appear to be from the records. It is interesting to note that the character of the effusion into the joints appears to correspond to that of pneumococcic peritonitis.

Dudgeon and Branson's cases strongly suggest that the "acute suppurative arthritis of infants," first described by Sir T. Smith, is usually due to the pneumococcus. Its frequent association with pneumonia and the clinical records, though deficient in the essential bacteriological examination, certainly point in this direction. The acute bone lesions of older children appear to be usually staphylococcic, but it seems worth an enquiry whether the pneumococcus is not an important organism in them and possibly in many pyæmic conditions so called.

That influenza sometimes causes joint trouble is an established fact, but it is difficult to say how common the infection is since so many minor ailments are called influenzal, and we know that the real disease may produce lesions of so many kinds and in so many organs. My impression is that it more commonly causes mischief in bones than in joints, but I have seen a young man with polyarthritis of the larger joints causing pain, and stiffness and muscular wasting. The arthritis was recurrent, and the joints did not quite recover. No absolute rigidity and no bony thickening were present. No other cause for the trouble could be found, and he had never been well since his first attack of influenza, but the inflammation of the joints did not come on for a year after the acute illness, so the cause is doubtful.

Prof. H. Marsh (in his Bradshaw Lecture) records two cases of severe inflammation of the hip-joint coming on in one case during and in the other after influenza. Œdema and pain seem to have been the prominent features.

Wallis (*Brit. Med. Jour.*, January 3rd, 1903) records a case in which many joints were affected at the time of the attack, but

the left knee alone remained troublesome, and ankylosis of the femur and tibia followed with fixation of the patella to the femur.

Dr. Murrell (*Lancet*, July 18th, 1903), relates a case of polyarthrititis affecting the middle-sized joints occurring after repeated attacks of influenza, and refers to the possibility of pneumococcic arthritis and of some cases attributed to gout being influenzal.

I have seen three other cases in which the hip became inflamed during an attack of influenza, and in one suppuration occurred, but as pneumonia was also present the question is doubtful, and unfortunately the record of the case is deficient. Brief notes of one of the other cases (Maggie G.) are appended :

Bacterial Arthritis (Influenzal).

Maggie G., æt. 15, was admitted to the Infirmary on February 12th, 1900. In October, 1898, she had influenza, "leaving her with acute rheumatism" which kept her in bed sixteen weeks. Both hips, knees and ankles were inflamed. All the joints recovered except the left knee which remained stiff. She was treated at Buxton for nine weeks in 1899. When she was in the Manchester Infirmary there was considerable loss of mobility of the left knee with some thickening of the synovial membrane, but no heat or tenderness. The joint could be flexed, but not fully extended. Extension and subsequent fixation were employed.

The following brief records illustrate some of the other various forms of systemic (bacterial) arthritis :—

Gonorrhœal Arthritis.

Mark K., æt. 28, ex-soldier, was admitted to the Royal Infirmary in June, 1907. His health was good till 1900, when he was invalided after a long march in the South African campaign on account of "flat feet." The feet were tender and the ankles swollen. No other joints were affected, and his health was good. No history of gonorrhœa is admitted. He served in India, and returned home in 1904 when he was laid up with swollen feet and ankles. He has never been well since. Subsequently he admitted that a "gleet" had ceased three

months before his admission to hospital. He had " remittent fever " in Rangoon in 1903. There was no syphilitic history. Three weeks before admission he suddenly fell ill, and then had pain in the left side followed by pain and swelling in the ankles, elbows, right shoulder, right sterno-clavicular and both temporo-maxillary joints. On admission, both plantar arches on both sides were tender and flattened. Both knee joints were distended with fluid, but beyond a sensation of weight were not painful. There was extreme tenderness in the right sterno-clavicular joint. Both temporo-maxillary joints were tender and swollen and painful on mastication. The teeth could not be separated more than $\frac{1}{2}$ — $\frac{3}{4}$ inch. Pus containing numerous diplococci was found in the posterior part of the urethra. The prostate was tender on rectal examination. All the symptoms improved under treatment.

Bacterial Arthritis (Staphylococcic Arthritis from Carbuncle).

Abraham U., æt. 38, was admitted in July, 1907. He stated that he had had no serious illness till last March, when he had a carbuncle on the back of the neck, which was incised and healed in about a fortnight. Three or four days later his right thigh began to be swollen, an abscess formed and was opened. He then had very severe pain in the left hip. The pain was so great that he could not bear any movement or pressure. Three days later the hip joint was opened by an anterior incision. He remained in the hospital in his own neighbourhood for two months. The discharge has never ceased, and the leg has become shorter and stiff. On examination at the Royal Infirmary the left hip was found stiff, adducted, flexed and inverted with about $\frac{3}{4}$ in. shortening. A sinus over the front of the hip led to bare bone. The discharge from the sinus was found to contain staphylococci. On exploration the sinus was found to lead down to the lip of the acetabulum, but no direct communication with the joint was found.

In this instance the nature and source of the joint infection is obvious. There was a local staphylococcic infection of the skin and subcutaneous tissue causing the carbuncle and a subsequent invasion of the right thigh and left hip joint. In the

latter the process was evidently a severe one leading to some destruction of bone.

Systemic Arthritis (Syphilitic).

Thomas B., æt. 32, ex-soldier. Seen May, 1907. In 1893 had Malta fever, later a chancre, but no secondary symptoms. In 1897 he had ague. For the last seven years has worked in Manchester, has had good health and has four healthy children. In May, 1906, the left ankle became swollen and painful, and at the same time a swelling appeared in the left parietal area. A month later the right shoulder and one ear became swollen and painful, and in August the left shoulder was attacked. A month before admission to hospital the right sterno-clavicular, left elbow and left knee joints were affected.

On examination, the liver and spleen were found to be slightly enlarged, otherwise the viscera were normal. Examination of the blood showed no abnormality. The pupils were unequal, but reacted naturally. The left ankle showed signs of old peri-arthritis with some stiffness, but no pain or grating. The left shoulder was in like condition. The right sterno-clavicular, left elbow and left knee joints were distended with fluid and very painful on the least touch or movement; the skin over them was hyperæmic, but not œdematous. The scalp over the left parietal area was adherent and thickened, with a definite raised margin to the swelling, which was very tender and constantly ached.

Under treatment by potassium iodide in doses increasing to 20 grains three times daily together with fixation of the joints of the limbs pain and swelling disappeared except from the sterno-clavicular joint, which was not immobilised. The symptoms tended to recur on movement or on ceasing to take the iodide. The gumma on the scalp subsided also and ceased to be tender or painful.

Notes by Dr. T. S. Harrison.

Autotoxic Arthritis.

In 1903 I saw, with Dr. Albrecht, a woman who had glandular abscesses in the neck in childhood, and in 1890 became anæmic and subject to neuralgia. In 1894 she began to have

pains in the hands, and about the same time had pleurisy, followed a year later by influenza. About this time also the patient had swollen feet and sores on the legs. The ulcers healed, but broke out again six months before my inspection of her. In 1899 the left elbow became swollen and stiff. The hands have remained in much the same condition, and no other joints have been affected. When I saw her the range of movement in the left elbow was limited to about 40°. There was effusion into the left wrist joint and adjacent sheaths. In the right elbow there was evidence of slight thickening of the synovial fringes. The head of the first left metacarpal was thickened, and there was snapping and cracking in both knees on movement; there was no jaw trouble. The condition of the joints was unaffected by weather or exercise. Menstruation had been irregular and somewhat painful. She had not been pregnant, had not had leucorrhœa or any urinary or intestinal trouble, nor had there been any throat or ear affection. At the time that I saw her she had ulcers on the back of the calf with cutaneous varices. I saw her again in March, 1904. The ulcers had then healed, but the joints were getting worse.

How is such a case to be labelled? The length of time since her health first began to fail made it difficult to fix the sequence of the various troubles. My own belief is that the joint lesions were due to absorption, probably from the ulcers, possibly from the uterus, but I cannot prove it. No doubt the name "rheumatoid" would be applied by those who use the term. It is noteworthy that in this case the joints got worse, though the ulcers healed, but an established joint lesion does not always get well or remain stationary when the original cause is removed.

Autotoxic Arthritis (Uterine).

On the same day that I saw the last case I also saw a woman of 43, Mrs. L., who sixteen years before had borne her youngest child. She had not been pregnant for seven years previously. After a simple confinement she got up early and began to have trouble with the left knee, which was swollen and stiff. The right knee, right wrist, fingers and ankles became consecutively affected. When I saw her the left knee was ankylosed in good

position, the right knee could be moved through 30° smoothly and was slightly flexed. The right wrist was stiff and the seat of periarticular swelling. There was fusiform swelling of the middle of the left index finger. Menstruation was frequent, and the joints were said to be always worse during her periods. It is interesting that this patient had seen many advisers, one of whom had proposed to open the left knee and promised a mobile joint as a result, while another equally eminent surgeon wished to fix the knee.

For cases of puerperal, menstrual and leucorrhœal arthritis—one of each—I may refer to a clinical lecture of my own, published in the *Lancet* for May 17th, 1902.

Autotoxic Arthritis (Puerperal).

Annie K., æt. 23, was admitted to the Royal Infirmary on March 17th, 1905. Her ailment began twelve months ago. She was confined and got up in a week; her labour was not a difficult one. A fortnight after her child was born she was suddenly taken ill with severe pains in the back, groins and down the legs to the feet. She was feverish, and her doctor "thought she had rheumatic fever." Menstruation has disappeared since her confinement. She did not suckle her baby. About five weeks ago some dark clots of blood were discharged from the uterus. She had night sweats and starting pains. On examination the right hip was flexed and stiff, and there was pain in the groin and knee and tenderness over the sacrum. There was thickening about the lower end of the right femur. There was no fever. The hip was manipulated under an anæsthetic, and she was discharged somewhat improved soon after.

Autotoxic Arthritis (Uterine, Leucorrhœal ? Bronchitic).

Matilda L., 35, married, was admitted to the Infirmary December 30th, 1903. Five years before admission she had a miscarriage, and has had leucorrhœa ever since. She has had no other pregnancy. Five months ago she had an attack of bronchitis, and was ill for a month. After being up for a week pain appeared in all her joints; the pain lasted two days and then disappeared from all the joints except the left knee which

became swollen and so painful that she has not been able to use it since. The knee was found swollen, with thickening round the bones. It was excessively tender and $3\frac{1}{2}$ inches larger in circumference than the fellow joint. Active movement was impossible, and passive too painful to be borne, but on attempting it a creaking sensation was felt. There was no constitutional disturbance. The left ankle was "dropped."

Massage and movement was the treatment adopted for the ankle and massage for the knee. A vaginal douche was used. She was sent to the Convalescent Hospital early in February. The swelling of the left knee had decreased, but it was still $1\frac{1}{4}$ in. larger than the other and still very painful on any attempt at movement.

This patient was a delicate woman "subject to asthma and a weak heart." It is doubtful whether the joint affection was due to absorption from the bronchial mucous membrane or from the uterus; its onset suggests the former, its persistence the latter.

From notes by Dr. Ollerenshaw.

Autotoxic Arthritis in a Tuberculous Patient.

Louisa B., æt. 24, single, was in the Infirmary in October, 1903. She gave a family history of tuberculosis, and was herself in the Children's Hospital for peritonitis, probably of tuberculous nature, when she was 7 years old. She has always been delicate. She has never menstruated, but has slight leucorrhœa of unknown duration. She has had a "swollen throat," but no serious illness except her joint mischief. About four years ago the knees began to swell and have been increasing in size ever since. About the same time the elbows began to get stiff. Some four months ago the wrists became swollen, and her neck began to get stiff three months ago. For the past few months there has been pain in the neck and knees each month; the pain lasts two or three days, and then disappears for a month when it recurs for two or three days, and so on. Until this time she had no pain, and apart from this she has had no indication of the menses.

On examination, both elbows are stiff as regards flexion and extension, but pronation and supination are free. Both knees

are full of fluid; the left measures 14 in., the right $13\frac{1}{2}$ in. in circumference. Both joints are in extension, but freely mobile without pain, but fine crackling is present on movement. There is no obvious bony change. The joints have been painful for six months. There is slight fulness of the left ankle. The muscles of both legs are wasted, and both are slightly swollen. The hips appear healthy. The left wrist is swollen and crackles on movement, which is painful, but not much restricted. The right wrist has more limited movement, but is otherwise like the left. Both elbows are ankylosed in a flexed position, though pronation and supination are free. It appears that the first sign of the elbow troubles was painless stiffness without swelling, which did not appear till between one and two years later, while in the knees swelling was the first sign noticed. While she was in Hospital about 2 oz. of serous fluid were withdrawn from the right knee by aspiration, and on examination microscopically and by cultivation by Dr. Sidebotham no organisms were found. Unfortunately after ten days' stay the patient contracted scarlet fever of which there was an outbreak in the ward at the time, and was removed to the Fever Hospital.

This is another complex case. Whether the condition was tuberculous or autotoxic or a mixed infection it is difficult to say.

Autotoxic Arthritis (probably Bronchitic).

Annie H., æt. 36, single, seamstress, was in the Infirmary in December, 1903. She told us she had always had a "weak bronchitic chest." She had had influenza several times; the first attack was five years before her admission. For the last eight years she had had trouble with her right knee every year. The joint became swollen and painful. Her last attack began in June after climbing. There was no illness except the bronchitis at the time of or immediately before the first joint trouble eight years ago, and she had no injury. During the first attack she was laid up for some weeks and the knee was swollen, hot and painful, but got quite well after a few weeks. The second attack was four years ago, when she was laid up for some weeks. Since then she has had pain in the knee every winter, but has been laid up only twice, each time with the same symptoms.

The knee was swollen and painful before she began to climb, but got worse afterwards, and she has been in bed since August, when she had a slight attack of "inflammation of the right lung."

Four years ago she was said to have ulcer of the stomach, and had "anæmia" six years ago. For the last two years she has had leucorrhœa.

On examination, the right knee was found much swollen with the joint outlines obliterated. The knee was fully extended, and the swelling did not appear to be due to fluid. There was very little active mobility of the joint, passive movement was very painful and the limb lay flaccid and toneless. There was thickening round the upper end of the tibia with prominence of the subligamentous fat pads and perhaps slight thickening round the femur. No obvious heat or redness of the joint, and no constitutional disturbance. The right ankle was slightly swollen, and the toes were pointed. There was profuse leucorrhœa at the time of admission; this soon got less after treatment.

This patient was in Hospital a month, and was treated at first by application of a splint with douching for the leucorrhœa, and iodide of potassium, and the joint was massaged at first once in three days and later daily. The swelling subsided a good deal and some mobility had returned on her discharge to the Convalescent Hospital.

The interest of this case is rather in the difficulty of assigning the correct cause than in finding a cause, and it is probable that more than one factor contributed. There can, I think, be little doubt that the joint mischief was due to absorption; it was an autotoxic arthritis; the local characters of the joint lesion were quite those of such an affection. The history indicates absorption from the chronically inflamed pulmonary mucous membrane as the starting point, and it is possible that the gastric and uterine disturbance as well as overstrain may have contributed to the later attacks.

Notes by Dr. Ollerenshaw.

Autotoxic Arthritis (Tonsillitis).

Edith S., æt. 12, was seen September 24th, 1907. She had

suppurative otitis in infancy, but recovered, and has had no ear trouble since. For years she has had tonsillitis, any exposure to wet or cold bringing on an attack. She has menstruated regularly since April, 1906. In October, 1906, her attendance at school entailed many wet walks, and at this time both her wrists became swollen and painful.

The mother was told the child had rheumatoid arthritis, and must winter for two years in a well-known health resort. She was also advised to have the tonsils removed; so probably the source of the joint trouble was recognised. The tonsils and adenoid vegetations were removed, and the general health, as well as the condition of the wrists, soon got better. She was seen in December, when, beyond a certain amount of swelling of the wrists, there appeared to be little wrong.

Traumatic Osteo-Arthritis (? Tubercle).

Elizabeth S., 22, single, admitted October 19th, 1904. When 7 years old the left knee was injured by a kick. The joint became swollen, but there was no pain afterwards for five years, when the joint became flexed and remained swollen until her admission to Hospital. On examination, the knee was slightly flexed and swollen on the inner side where there was a ridge of bone corresponding to the articular border of the tibia. There was considerable mobility, but with marked grating, and the movements of the patella were restricted. The joint was opened by the transpatellar method, and it was found that the cavity was practically obliterated and its place taken by thick fibrous bands. There was no pulpy thickening and no caseation. There was some growth of bone on the articular surfaces which were devoid of cartilage in places, while over the condyles of the femur fibrillation of cartilage was present. The case was apparently regarded as a tuberculous one, but microscopic examination of the tissue removed failed to show proof, and there was no caseation. The patient's history did not suggest tubercle, and her only illness appears to have been "inflammation of the bowels" at 19 years of age. She recovered well from the operation.

The case is introduced here to illustrate the fact that osteo-

phytic outgrowth with fibrillation of cartilage and eburnation of bone are conditions not limited to "rheumatoid arthritis," but may occur in a case which may have been tuberculous or may have been simply traumatic.

Metabolic or Trophic Arthritis (Gout).

Thomas G., æt. 46, was in Hospital in May, 1903. Seven years before admission he was laid up for nine weeks with inflammation of both knee joints, which he attributed to constantly knocking them at his work. Since that time he has never been able to walk properly. The right knee was said to become swollen and very painful whenever he knocked it or knelt upon it. He has been frequently laid up for a fortnight on account of it. His general health was good. On examination of the right knee it was found slightly swollen, very painful if he stood on it or bent it, and there was crackling on movement. The man was very positive that the condition was entirely due to his work, and he was so much crippled by it that, on the assumption that the trouble was probably due to localised thickening of the synovial fringes, the joint was opened, on May 29th, by a transverse incision below the patella. The appearance of the interior of the joint was remarkable; it looked as if the joint had been injected with white paint which not only covered the articular surfaces, but infiltrated in lines the ligaments around, including the ligamentum patellæ. The urate of soda, of which the paint-like substance consisted, was scraped and washed away as far as possible, but much of it remained behind. The joint was closed, and though there was some rise of temperature for ten days, he recovered, and was discharged on June 22nd. He was seen again in October, and still complained of pain on movement of the joint or if he put weight upon it, and he is better while he wears a back splint. He then told us that he had swelling of the knuckles some four years previously; this was also attributed to injuries. Both knees were still tender and the knuckles were then red and slightly swollen. The history of this case was somewhat complicated by the desire of the patient to obtain a certificate that his troubles were due to his work.

In December, 1907, Dr. Bury kindly showed me in his wards a man of 52, with a strong family history of gout. The patient was a publican, and had tophi in his ears. Without going into detail, he may be said to have had many attacks of joint inflammation during the past twenty years. At the time of his last admission both ankles were somewhat swollen and stiff. Both knees were swollen, and showed well marked osteophytic outgrowths, and on movement, which was fairly free, it was evident that the synovial fringes were thick and nodular. The first interphalangeal joint of the right ring finger was the seat of fusiform swelling with stiffness. The temporo-maxillary joints were not apparently affected. He had gonorrhœa twenty years ago. No source of infection had been found when I saw him, and it seemed probable that gout had some share in his arthritic troubles, but that probably some other element which we did not discover also participated. X-rays showed only blurring of outline of the joint margins with cloudiness of the cartilages.

The foregoing brief notes of a somewhat random selection from among the various forms of arthritis which necessarily come under the notice of those who work long in a large hospital are put together rather as suggestions than as complete records, but even so much would not have been possible without the kind assistance of my colleagues in asking me to see, from time to time, patients under their charge. To them I offer my best thanks. Among those colleagues perhaps no one took a greater interest than did Dr. Dreschfeld in the more obscure varieties of joint lesion, and had his life and power of work continued we might well have looked to him for help in clearing up the confusion in which the nomenclature and arrangement of diseases of the joints at present remains.

Should circumstances permit it is hoped on a future occasion to enlarge the record of cases of which I have more or less complete notes, and to collate the references to published papers illustrative of some of the conditions to which reference has been made.

THE SUPERVENTION OF EPITHELIOMA UPON LUPUS VULGARIS.

By ROBERT B. WILD, M.D., M.Sc., M.R.C.P.,

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Hospital.*

It has long been known that scar tissue is a favourable site for the development of malignant disease, and many papers have been written upon the subject since 1852, when Dr. James Reid, in the *Provincial Medical Journal*, wrote his excellent paper upon the "Identity of Warty Ulcerations of Cicatrix with Epithelial Cancer," and described a number of cases in which the growth was squamous epithelioma and the clinical course similar to what we see at the present day. The marked proclivity of the scars of lupus vulgaris to these growths was specially noted by Mr. Jonathan Hutchinson, and a typical case is described and figured in the *Archives of Clinical Surgery*, vol. ii. Other cases have been described, notably four by Dr. Norman Walker in the *Scottish Medical and Surgical Journal* for 1904, which occurred in patients who were under X-ray treatment for lupus vulgaris.

My reasons for bringing forward additional cases are, firstly, that I believe this terrible complication of lupus vulgaris to be more frequent than is generally supposed; secondly, that there is a marked family likeness in all the reported cases of this character, and certain peculiarities in their mode of onset and clinical features seem worthy of careful study as likely to throw light upon the wider problem of the etiology of malignant disease in general; thirdly, I do not know of any cases hitherto published that have been followed to their termination, and in which it was possible to compare cases treated by X-rays with older cases not so treated.

Mr. Malcolm Morris, in his *Text-book on Diseases of the Skin*, remarks that "as a class sufferers from lupus are not

long-lived," and this statement is borne out by the statistics of my cases at the Manchester and Salford Skin Hospital. From January 1st, 1894, to May 23rd, 1906, I have notes of 20,000 cases, of which 413 (2 per cent.) were tubercular—excluding 104 cases of lupus erythematosus. Lupus vulgaris accounted for 290 (1·45 per cent. of all cases), tuberculosis verrucosæ cutis for 40, and other tuberculous lesions for 83. Of the lupus vulgaris cases 134 were males and 156 females, and the age distribution was as follows:—

Under 15 years of age, 98 cases.

Over 15 and under 25, 102 cases.

1 case developed epithelioma.

Over 25 and under 35, 40 cases.

Over 35 and under 45, 29 cases.

Over 45 and under 55, 10 cases.

Over 55 and under 65, 7 cases.

Over 65 4 cases.

5 cases of epithelioma.

Thus only 50 cases were of age 35 and upwards, and of these 5 (10 per cent.) developed epithelioma. The oldest case of lupus vulgaris was aged 81; the disease had lasted 70 years and was still active in places; there was no epithelioma in this case, though the scarring covered large areas and the nose and both eyes were completely destroyed.

In addition to the six cases from the Skin Hospital three cases have been under my care at the Christie Hospital. For the sake of brevity in the following account of these nine cases only the points bearing upon the special lesions are given:—

CASE I. Eliza A.D., spinster, aged 68. Admitted to Christie Hospital August 14th, 1893. Died December 19th, 1893.

As a child she had lupus vulgaris of the face, which was partially restrained by treatment, but repeatedly ulcerated up to the age of 37. The scarred condition which resulted from the disease remained practically unchanged for thirty years.

About twelve months before admission an ulcer appeared on the upper part of the right cheek and spread rapidly. A few months later a second ulcer appeared on the lower part of the same cheek.

On admission the face presented a typical lupus scarring over both cheeks, the lower part of the forehead and the right side of the neck; the tip and alæ of the nose and part of the right ear were deficient. The lower eyelids were drawn down and everted by the scarring of the cheeks, and there was an opacity on the right cornea. The upper part of the right cheek presented an extensive, irregular ulceration with raised hard edges, a nodular base and a foul discharge. It extended from one inch anterior to the right external auditory meatus to the left side of the bridge of the nose, and from the edge of the lower eyelid almost to the level of the upper lip; at the lower anterior corner a sinus penetrated into the buccal cavity. Below this ulceration and separated from it by nearly an inch of healthy scar tissue was a second ulceration about one-third the area of the first and extending almost to the lower margin of the jaw.

On October 10th an independent nodule was noticed above the larger ulceration and just posterior to the external angular process of the frontal bone; this nodule soon formed a third ulceration.

The growths spread rapidly, and by the beginning of December had coalesced and destroyed the whole of the right side of the face. The patient died from exhaustion on December 19th.

There was no enlargement of any lymphatic glands, no secondary visceral growths were found at the post-mortem, and microscopically the growth was a typical squamous epithelioma.

CASE II. John M.G., rope maker, aged 44. Admitted to Christie Hospital November 5th, 1896. Died July, 1897.

Lupus vulgaris of the face since a child; commenced work at a rope-walk at the age of 8; was a patient of the Manchester Royal Infirmary at 16 for nearly two years.

About nine months before admission he noticed a hard "pimple" on the left cheek which gradually enlarged and ulcerated. A month later he scratched the right cheek and the slight injury did not heal, but gradually extended to form an ulcer with hard edges. He was treated at the Skin Hospital by Dr. Brooke, and shown as a case of epithelioma on a lupus scar at a clinical meeting of the Manchester Medical Society. He did not improve, and was sent to the Christie Hospital.

On admission the lower two-thirds of the face was formed of scar tissue and the lips were much thickened. On the right cheek was an irregular ulceration about two inches in diameter; the centre of the ulcer was on a level with the commissure of the lips, and the anterior edge reached to within half an inch of the angle of the mouth. The margins were indurated and slightly raised, the base hard and nodular; there was a slight discharge.



Fig. 1, Case 2.—Old lupus scar. Epithelioma of rodent ulcer type on each cheek.



Fig. 4, Case 6.—Recurrent epithelioma on lupus scar; fungating type; extending towards chin by fresh growths in scar.

On the left cheek just outside the ala of the nose there was a smaller ulceration of similar character and about two-thirds the size. (Fig. 1.)

He left the hospital at his own request, and was re-admitted February 8th, 1897, when the growths had considerably extended; the ulceration on the right side now involved both lips. There was no enlargement of the lymphatic glands.

The growths spread rapidly, and he finally died in the Union Hospital in July, 1897.

CASE III. John M., blacksmith, aged 37. Admitted to Christie Hospital July 21st, 1897. Died November 15th, 1898.

Mother died from phthisis. History not clear as talking was very difficult for him, but the scarring of the left side of the face, the dragging downward of the left lower eyelid, the destruction of the lower part of the nose and the cicatricial remains of the left ear showed that there must have been extensive lupus in early life.

The ulceration, which he still called lupus, commenced in April, 1895, at the left side of the upper lip near the nose. He was operated upon by Mr. Southam at the Manchester Royal Infirmary, who removed the growth and transplanted a flap of skin from the left arm to fill up the deficiency in the upper lip.

On admission there was a fluctuating swelling of the left cheek near the upper lip; this soon broke down and disclosed a large cavity opening into the mouth and nasal fossæ. The anterior part of the hard palate, the vomer, turbinated bones and left superior maxilla were partially destroyed. The margins of the cavity soon became hard, raised and nodular except below, where the transplanted flap from the arm formed the boundary and was never infiltrated by the growth. As the ulceration extended this flap was separated as a whole.

The destruction of tissue by the extending growth proceeded slowly, but at the time of his death, sixteen months later, of the whole face only the forehead, right eye and lower jaw remained. There was no enlargement of the lymphatic glands. No secondary growths in the viscera were found at the post-mortem, and microscopically the growth was an epithelioma.

CASE IV. Sarah W., married woman, aged 42. Admitted to Christie Hospital July 19th, 1897. Died in the Hospital May 3rd, 1904.

Lupus of the face since childhood, intermittent treatment up to the present time. For several years she has had a "wart" below the chin on the left side which has gradually increased in size.

On admission the whole of the left side of the face and neck was covered by lupus vulgaris with superficial ulceration due to pus infection; abundant apple-jelly nodules round the margin of

the diseased area. There was a similar patch on the crown of the head, and some cicatrisation of the nose and left ear. Below the chin, on the left side, was a hard oval growth $1\frac{1}{2}$ inches long, 1 inch wide and $\frac{3}{8}$ inch high; the surface was papillomatous. The growth was excised and microscopically examined; it was found to be a papilloma, though one part of the section showed a suspicious downgrowth of epithelial processes with a few cell-nests, which were, however, in the superficial layers of epithelium.

After recovery she was transferred to the Skin Hospital, and remained under treatment for lupus as an out-patient. Her attendance was irregular, but she slowly improved until January 31st, 1900, when a fresh growth of a fungating character was found on the scar of the previous operation. After temporary improvement by caustics it relapsed, increased rapidly, and she was again admitted into the Christie Hospital. The growth was widely removed on June 25th, 1900, and though much scarring resulted there was no recurrence on this site.

Again an out-patient intermittently at the Skin Hospital until June, 1901, when a papillomatous growth was found on the centre of the left cheek. She was put under X-ray treatment July 9th, 1901. After six months' treatment the papilloma had disappeared, and the lupus was greatly improved. Treatment was stopped January 25th, 1902. She returned to the Hospital March 17th, when a warty condition was again found on the centre of the left cheek. Treatment was resumed with closer applications of the tube. Some burning followed, but soon subsided, and the warty patch completely disappeared. Treatment was continued for the lupus, which, though much improved, was still very extensive, until on March 18th, 1903, a fresh warty growth was found on the left cheek. In view of the previous result the X-rays were pushed, and by May 30th a typical and painful burn resulted, and the treatment was stopped; the warty growth had completely disappeared. For four months there was no sign of healing, but by December, 1903, that is, seven months afterwards, two-thirds were healed. Towards the end of this month, however, a fresh growth of fungating character was found on the parotid region and below the left ear, posterior to the former growth and to the site of the X-ray burn. The X-rays were applied to the fresh lesion, but after a fortnight it was found that it was extending rapidly. She was again admitted to the Christie Hospital, and the growth removed February 8th, 1904. It recurred immediately, and was treated by formalin, but without any benefit. The growth spread rapidly over the face and neck, and she died from exhaustion May 3rd, 1904.

There was no enlargement of the lymphatic glands. At the post-mortem no secondary growths were found in any part of



Fig. 2, Case 5.—Recurrent epithelioma on nose. Lupus vulgaris on nose and both cheeks.



Fig. 3, Case 5.—Later stage. Nose well; lupus on cheeks improved; epithelioma on right cheek, with extension downward.

the body. The growth was shown microscopically to be a squamous epithelioma.

CASE V. Olivia W., married woman, aged 46. Admitted to Christie Hospital October 5th, 1900. Died July, 1903.

Suffered from lupus vulgaris of the nose and cheeks for over twenty years. During the last twelve months the skin over the lower part of the nose has become hard, fissured and painful. In June she became an out-patient under me at the Skin Hospital. Both cheeks were covered by typical lupus vulgaris; the nose presented a scabbed appearance over the lower third, and beneath the scab was a hard irregular shallow ulceration with well-defined edge. No improvement was produced by treatment, and she was transferred to the Christie Hospital, where the ulcer was removed under chloroform by a sharp spoon, and the thermo-cautery freely applied to the whole area. The wound healed well, and she was discharged November 8th, 1900. She remained well until September, 1901, when a fresh ulceration of epitheliomatous character was found on the nose. (Fig. 2.) On October 6th, 1901, she commenced treatment by the X-rays, and by the middle of April, 1902, after a sharp reaction, the nose was quite healed. The lupus had considerably improved, and at her own request X-ray treatment was resumed at the end of May, 1902, for the cheeks. This was continued at intervals during the year. There was a sharp reaction, especially on the left cheek, which, however, healed easily after a period of rest, and the lupus greatly improved. On December 3rd, 1902, the centre of the right cheek presented a papillomatous growth, which quickly broke down to form a shallow circular ulcer with hard edges and a nodular base, and two smaller ulcerations appeared below the first. During the next three weeks X-rays were applied to the new growth, but without checking the extension, and the treatment was stopped January 12th, 1904. (Fig. 3.) On March 11th she was again admitted to the Christie Hospital, and the whole of the growth freely excised. The wound never healed, fresh nodules appeared from the base, the edges became hard and nodular and spread rapidly by the formation of fresh nodules in the surrounding skin, so that by the middle of May, 1903, the whole right side of the face was involved and part of the neck.

The patient died at home in July, 1903. There was no enlargement of the lymphatic glands. The growth removed was a squamous epithelioma.

CASE VI. Edward W., metal finisher, aged 48. Admitted to Skin Hospital October 14th, 1903.

Lupus vulgaris of the face and neck since childhood. Several years ago he had a warty growth on the right cheek in front of the ear. This was excised at the Salford Royal Hospital.

Recurrence took place after a few months, and it was again excised, only to recur and necessitate a third operation six months ago. Three months before admission a warty growth appeared at the lower edge of the operation scar just below the angle of the jaw, and has grown rapidly. He presented lupus vulgaris with superficial scarring over the whole of the face below the level of the eyebrows and extending on the right side of the neck to the level of the clavicle. On the right cheek are the scars of his three operations, and below the angle of the jaw a raised hard growth about 2 inches in diameter and half an inch in height.

As he objected to further operation, he was at once treated by X-rays, and though the extension of the growth was checked it did not diminish.

On February 3rd, 1904, I took him into hospital. Formalin was applied, the mass of the growth removed, and the X-rays continued to the base. By March 5th the growth had gone and a healthy ulceration only remained. On April 6th there was slight induration below the ulcer, and on the 22nd recurrence was evident. The X-rays were resumed, but the fresh growth has continually extended, and there are now signs of fresh nodules anteriorly along the angle of the jaw. (Fig. 4.) These rapidly coalesced with the main portion of the growth. As the X-rays were doing no good and possibly might do harm, they were stopped, soothing antiseptic lotions applied and the growth gradually extended until he died at home from exhaustion in the autumn of the same year.

CASE VII. Albert M., æt. 18, factory operative.

Lupus vulgaris on the centre of the left cheek from the age of 3. Operated on twice at home when 5 years of age, again in Liverpool at 7, twice in the Wigan Infirmary at 13 and 14. Patient at the Manchester Skin Hospital in September, 1901, when 16 years of age. There was extensive scarring on the left cheek, chin and left side of the neck. Active lupus vulgaris at the edges of the scar and on the nose, which was stated to have been first attacked three weeks before. Large healed scars on the flexor surface of the left leg, and still active lupus behind the left knee and on the ankle (Fig. 5.) In December, 1901, treatment by X-rays was commenced and continued rather irregularly owing to illness at home and intervals for rest during 1902 and 1903. In December, 1903, he had a dermatitis from X-rays which resulted in a slight burn. No further sittings were given, and the surface was completely healed in March, 1904. He was seen on May 11th, 1904, and the scar was healthy.

On June 25th, 1904, he came to the Hospital with what appeared to be a small carbuncle with a black central slough on the lower part of the left cheek and below the scar of the X-ray burn. He looked ill, and his temperature was 100°F. Under



Fig. 5, Case 7.—Lupus vulgaris with extensive scar. Before X-ray treatment.



Fig. 6, Case 7.—Three years later. Lupus much improved by treatment. Epithelioma on lupus scar; fungating type.

treatment by boracic fomentations, etc., the inflammatory lesion settled down, but on July 27th the site of the carbuncle presented a raised papillomatous appearance. He then remained at home under his own doctor, and was not seen until September 17th, when the growth was larger, hard, and presented a painful ulceration in the centre. On October 24th, 1904, the epitheliomatous character of the growth was very evident; it was $2\frac{1}{2}$ inches in diameter and $\frac{3}{4}$ inch in height (Fig 6.) Operation was refused by the patient and his friends, though urged upon them as soon as a papilloma was found. He left the Hospital at the end of January, 1905. The growth rapidly spread over the face and neck, and he died at home in July, 1905. No secondary lesions were found in the glands while under observation. As excision was refused no microscopical examination was possible, and there was no post-mortem examination.

CASE VIII. John K., æt. 65, blacksmith. A broken-down old man; cataract in both eyes, the left operated upon with fair result. Lupus vulgaris on the face for over 20 years. Extensive scarring of the right side of the face with flat patches of superficial lupus vulgaris, and well-marked nodules on the cheek and right side of the nose. He had had no light or X-ray treatment. On the right molar bone in the scar tissue was an ulcer $\frac{1}{2}$ inch in diameter with hard raised edges and a suppurating base, a history of two months' duration and the application of irritating ointments. He refused operation, and was put under X-rays February 24th, 1904. On November 16th, 1904, he was discharged healed. Next seen June 28th, 1905, when the ulcer had again broken down and was somewhat larger than when first seen. The X-rays were resumed, but he was very irregular in his attendance. The ulceration continued and spread, and he ceased to attend in September, 1905. I have not heard directly from him since, and was told by a patient from the same neighbourhood that he was dead. There were no secondary deposits in the cervical glands.

CASE IX. William R., 38, farmer, strong and healthy. March 3rd, 1906, came to Skin Hospital. Since childhood had lupus vulgaris of the face and neck; typical scar present over the whole of the left side of the face, lower part of the ear, chin and neck to beyond the middle line. The scar presented scattered lupus nodules, and there was active disease at the edge, especially on the left side of the nose, on the chin below the mouth and on the neck to the right of the middle line. No X-rays or light treatment. Over the lower part of left cheek and upper part of the neck (almost the centre of the lupus scar) was a large ulcer 4 inches in diameter, edges raised, nodular and hard. Base irregular and with a sanious, foul-smelling discharge. He stated that the ulcer began like a boil in the summer, and had been rapidly enlarging during the last two

months. Treated for a month with carbolic dressings and then put under X-rays, which were continued—with intervals for rest—for four months. At first the effect was good and the more superficial parts of the ulcer healed irregularly, so that we had a scar with a number of smaller isolated epitheliomatous ulcers. Later on, however, these began to spread and coalesced. The X-rays were stopped April 17th, 1907, and since then he has had merely carbolic lotion to cleanse the parts and a boric acid ointment, with morphia internally.

I saw him October 19th, 1907, and the ulceration now occupies more than half the face, the cavity of the mouth is opened up and the lower jaw dissected out; the left ear is gone and the neck invaded to the middle line behind and almost to the clavicle in front. He is much weaker and will probably live to about Christmas.* No secondary lesions in the cervical glands.

In considering these nine cases certain points arise which seem to be worthy of further consideration. These are:—

(1) The etiology of the epitheliomatous growth. In several cases there was a history of slight trauma or mechanical irritation of the scar at the site where the growth subsequently appeared. In three cases an inflammatory lesion, due apparently to pus infection, was seen and treated, and its subsidence followed by a papillomatous growth which became epitheliomatous. In three cases the growth appeared on an area which had been, or was being, treated by X-rays, though not actually on the site where the greatest reaction had been produced.

(2) The character of the lesions. In all those seen at the commencement the lesion was primarily of a papillomatous character, and in most of the others the earliest lesion noticed by the patient was of this type. Ulceration commenced in the centre and the edges gradually became indurated, and from this point onward two distinct types are found—one of a fungating character with rapid spread and formation of a growth of considerable size, the other breaking down into deeper ulcerations in which destruction almost kept pace with new growth. These latter cases were less rapid in their progress, and in their later stages were not easy to distinguish clinically from rodent ulcer.

(3) The tendency to form multiple lesions or successive lesions on different parts of the lupus scar, and for the disease to

*The patient died January 7th, 1908.

spread by the formation of fresh foci in the apparently healthy scar tissue beyond the margins of the primary growth. I am inclined to look upon these later lesions as mostly due to transplantation of epitheliomatous cells from the breaking down primary growth on to the scar tissue. In several cases, however, the multiple lesions were apparently independent growths, and it is not difficult to conceive that the whole of the tissues in a lupus scar may be in a state of unstable equilibrium, so that any exciting cause of cell proliferation—whether mechanical irritation, parasitic invasion, or ethereal vibrations—may disturb the balance between epithelium and connective-tissue and determine the onset of a malignant growth at one or at several points.

(4) The absence of secondary deposits in the lymphatic glands, though the growths were microscopically squamous epitheliomata and usually rapidly growing. In the cases examined post-mortem secondary visceral growths were also absent. The natural explanation of this appears to be the destruction of the lymphatics by the preceding lupus and the possibility that the scar tissue with its slight vascularity contains no lymphatic vessels capable of transmitting the comparatively large epithelial cells to the nearest glands. In one case, however, the epitheliomatous infiltration was found post-mortem to have extended into and infiltrated the underlying muscle tissue and yet the glands were unaffected.

(5) The effect of the X-rays. Three of the nine cases (i., ii. and iii.) occurred before the discovery of the X-rays, the course of the disease was the same as in the later cases and in one of them the destruction of tissue was the greatest I have ever seen. Three other cases (vi., viii. and ix.) were well developed epitheliomata when admitted to the Hospital, and were treated by X-rays with temporary benefit; one healed up after nine months' treatment, but broke down again some five months later; in the other two the benefit was very transitory, and the treatment was stopped as the growth was rapidly extending. In the remaining three cases (iv., v. and vii.) the patients were treated by X-rays for lupus vulgaris, and the growths appeared upon the surface of the treated scar. Case iv. had a papillomatous growth, recurring after removal before any X-ray treatment was

used. The growth which eventually caused death was on a different site it formed before and was twice removed by the X-ray treatment, only to recur later and spread in spite of X-rays pushed to the limit of reaction. Case v. also had an epitheliomatous lesion on the nose, recurring after operation and healed by X-rays without subsequent recurrence. The growth eventually fatal formed on the right cheek, and it is worthy of note that the only marked reaction to X-rays was on the left cheek. Case vii. was unusual in the early age of the patient; he was treated for a considerable time, and an X-ray reaction was produced on the left cheek; the subsequent epithelioma formed just below this and not where the reaction had been most severe. It is not possible to say in these three cases whether the X-rays had any part in the production of the epithelioma. If so then it appears as if a special intensity of radiation was needed, something more than a therapeutic dose and something less than sufficient to produce an X-ray burn. One thing, however, is certainly demonstrated by these three cases, viz., that the X-rays employed for the treatment of the lupus had no prophylactic value in preventing the formation of epithelioma.

(6) Finally, I wish to emphasise the importance of warning all middle-aged patients with lupus scars of the necessity of at once applying for treatment should the scar show any tendency to a warty formation or ulceration. Superficial lesions of this character may be treated by X-rays as in several of the above cases, but usually recur, and the same may be said of surgical removal. I believe, however, that an immediate and complete excision—even though the operation has to be carried out through scar tissue—offers the best chance of cure, and in any case prolongs the life of the patient and affords a period more or less prolonged before the growth recurs or a fresh lesion appears.

THE SURGICAL TREATMENT OF LABYRINTHINE SUPPURATION.

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THE vast majority of cases of labyrinthine suppuration are secondary to chronic, more rarely acute, septic disease of the middle ear. The most frequent paths of infection from the one cavity to the other are:—

- (1) Through a fistulous tract in the external semi-circular canal.
- (2) Through the fenestra ovalis.
- (3) Through the fenestra rotunda.

In only from 1 to 2 per cent. of cases of chronic septic otitis media does labyrinthine infection result. This no doubt is due to the denseness of the bone forming the labyrinthine capsule, and to the rigidity of the annular ligament and the membrana secundaria.

Once septic infection has gained access to the internal ear there is nothing to prevent its passage to the base of the brain or to the surface of the cerebellum.

The various paths along which pathogenic organisms travel brainwards are the perivascular sheaths of the auditory or facial nerves, the aqueductus vestibuli, and in exceptional cases by erosion of the superior semi-circular canal. Another path of infection is at times possible, viz., by transference of organisms along Mouret's canal, a canal running from the posterior wall of the mastoid antrum through the pars petrosa and opening upon the posterior wall of the pyramid above the internal auditory meatus. (Fig. 1).

The surgery of labyrinthine suppuration has received a great impetus from the writings of Lermoyez², Gradenigo¹², Friedrich¹¹, Jansen¹, Hinsberg³, Botey⁵, Bourgouet¹⁹ and others, yet it may be said to be still in its infancy.

Various operative procedures have been devised for the

purpose of exposing the area of disease and for eradicating, if possible, the foci of infection.

Whatever means be adopted to open up the labyrinth, the first, and an essential, step is the performance of a "complete radical mastoid operation" with a free and generous removal of the facial spur. (Fig. 2.) In this way the outer labyrinthine wall is brought fully into view, and under a powerful illuminant fistulous tracts are carefully looked for. A word of caution is necessary here, as it is very easy to mistake the opening of a minute bone cell for the mouth of a fistulous tract. A very careful examination with a probe is essential under such circumstances.

The main practical difficulties experienced in opening up the labyrinth are due to the anatomical disposition of the following structures: the facial nerve, the internal carotid artery, the jugular bulb and the superior petrosal sinus.

If during the performance of the radical mastoid operation the facial spur be freely cut away the position of the fenestra ovalis and the fenestra rotunda is readily demonstrated.

The horizontal semi-circular canal is invariably situated 3 mm. above the Fallopian aqueduct, and is usually separated from it by a small furrow in the bone. Occasionally, however, the one merges imperceptibly into the other. The general direction of the external canal is oblique, and not horizontal as its name would imply. (Fig. 3.) Its anterior arm is 5 mm. in length, and opens into the posterior wall of the vestibule by a dilated orifice. This opening is $1\frac{1}{2}$ mm. above the Fallopian aqueduct, or $4\frac{1}{2}$ mm. above the fenestra ovalis, and is found in a vertical line drawn through the posterior border of the oval window. The posterior branch opens also upon the posterior wall of the vestibule.

The anterior branch is situated almost invariably above the facial nerve, but in a certain proportion of cases—estimated at about 12 per cent.—it occupies a lower position and is crossed by the facial nerve.

Various methods have been suggested for opening up the interior of the labyrinth.

Jansen, to whom the credit of having first opened the labyrinth

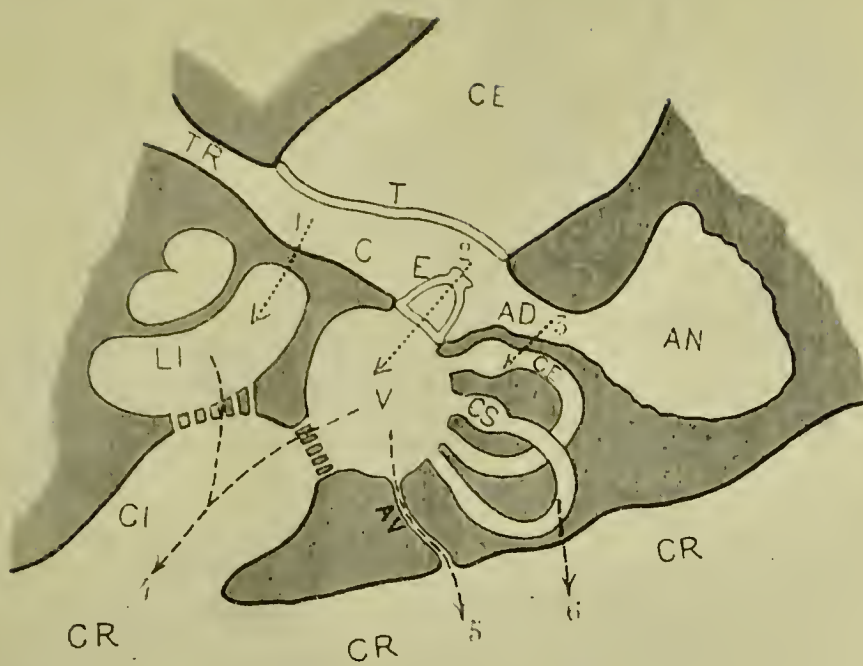
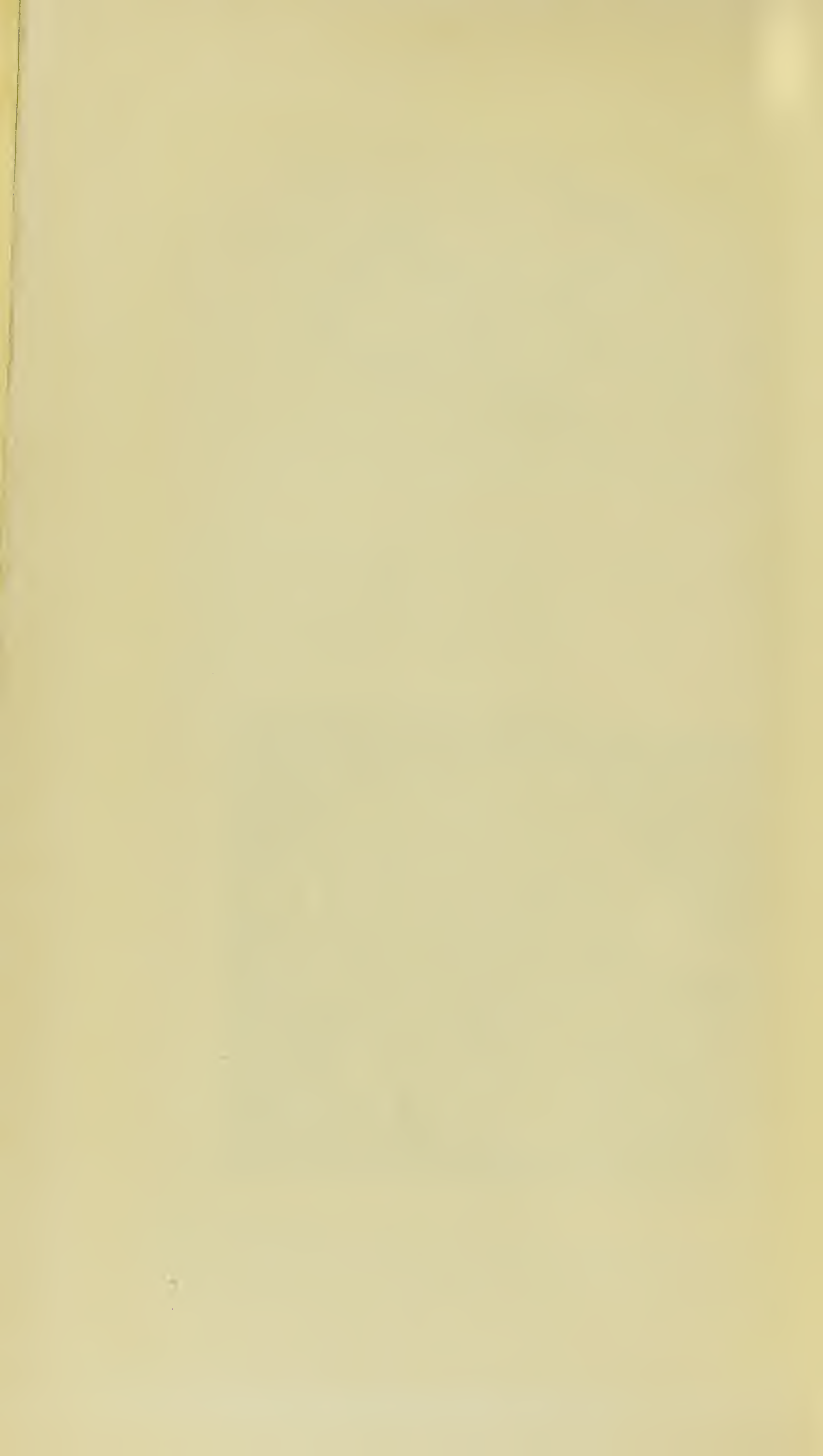


FIG. 1.—Diagrammatic view (after Lermoyez) of the usual routes of septic infection from the middle to the internal ear (1, 2, 3) and from the internal ear to the interior of the cranium (4, 5, 6). CE, External meatus; T, membrana tympani; AN, mastoid antrum; LI, cochlea; V, vestibule; AV, Aqueductus vestibuli; GE, external semicircular canal; GS, Superior semicircular canal.



FIG. 2.—Complete radical mastoid operation with view of outer labyrinthine wall. The horizontal, superior and posterior semicircular canals have been opened up to show their relative positions. The aqueductus Fallopii has also been freely opened up. A portion of the posterior (bony) meatal wall has been left intact.



is due, performs a complete radical mastoid operation, and freely exposes the outer labyrinthine wall. The posterior branch of the external canal is located and opened. By working in a direction forwards and upwards its anterior branch is followed into the vestibule. The opening thus made is carefully enlarged, great care being taken to avoid wounding the Fallopian aqueduct which in normal cases is situated $1\frac{1}{2}$ mm. below the ampullary orifice of the anterior branch of the external canal. In performing Jansen's operation care must also be taken to avoid injuring the dura mater and the superior petrosal sinus above and the jugular bulb below.

Botey opens the vestibule by taking as his immediate landmark the anterior limb of the external canal, opening it and enlarging the opening thus made anteriorly and superiorly. Should the stapes happen to be still *in situ* he removes it, if not he opens the fenestra ovalis and cuts away the posterior portion of the pars promontoria between the two fenestræ.

In this way an opening is made both in front of and behind the curve of the Fallopian aqueduct.

Hinsberg, after a complete and radical mastoid operation, opens the fenestra ovalis by the removal of the stapes if still present. The opened fenestra is carefully enlarged in an upward direction. A small stylet is then introduced into the vestibule as a guide, and the bony covering of the anterior limb of the external canal is cut away until the stylet is exposed to view.

The Bridge Operation.

The operation which I have performed in 10 cases of severe labyrinthine suppuration and which has given excellent results is as follows:—A complete and radical mastoid operation is first performed, and in order to secure free access to the whole operation area the following method of making a flap from the soft parts is adopted:—A long knife is introduced into the meatus and made to cut vertically outwards along the line of junction between the superior and posterior cartilaginous walls of the meatus. The incision is carried well into the concha. The knife is now swept round in a circular direction parallel to the curve of the anti-helix to the floor of the meatus. The comparatively large flap thus secured is trimmed, and folded

downwards and backwards on to the floor of the excavated mastoid process. The flap is kept in position by two silkworm strands passed first through the skin of the neck, then through the flap and back again to a point close to the original point of entry and tied over a rubber tube. The petro-mastoid is now entered in the triangular space between the posterior limb of the external canal and descending limb of the posterior canal. This little triangle is situated 4 mm. behind the highest point of the extreme convexity of the descending portion of the Fallopian aqueduct.

The opening thus made is enlarged upwards and backwards until the posterior canal is freely opened. By now working forwards along the external canal its anterior limb is opened, and by following this the vestibule is ultimately reached.

A special "facial protector" (fig. 4) is now inserted and lies over the aqueduct in the form of a cap. The fenestra rotunda is then located, opened by means of a small bur and the pars promontoria cut away in an upward direction until the fenestra ovalis is reached, the stapes being removed if still present. By means of a specially-constructed bur cutting vertically the bone lying immediately under the aqueduct is cut away, so that finally, when the facial protector is removed the aqueduct appears like the arch of a bridge—end on, as it were, and facing the operator—between the semi-circular canal system behind and the cochlear system in front. (Fig. 5.)

Free drainage of the various segments of the internal ear is thus effected whilst the cavity is allowed to granulate, and finally to obliterate itself.

After the completion of the operation and when the auricle has been put back into position (not necessarily sewn back) the edges of the incised concha are trimmed in such a way that when the finger is placed in the enlarged meatus its edge is found to be on the same level as the floor of the exenterated mastoid.

In illustration of the above remarks the following three cases are cited :—

CASE I. E. M., aged 35, had suffered from chronic suppurative middle ear disease for twenty years following a severe attack of scarlet fever. Attacks of deep-seated pain in and around the affected ear had been fairly frequent during a period of nearly twelve months prior to his admission to hospital. The more recent attacks of pain had been accompanied by sickness

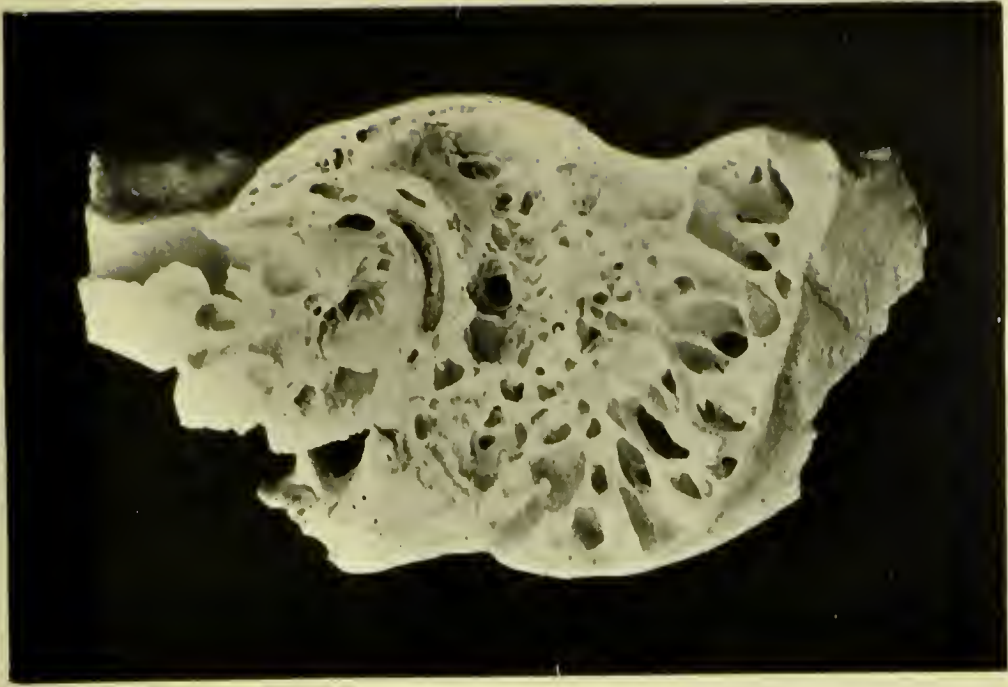


FIG. 3.—Section of temporal bone to show the relative positions of the fenestra ovalis, the Fallopian aqueduct and the horizontal semicircular canal.

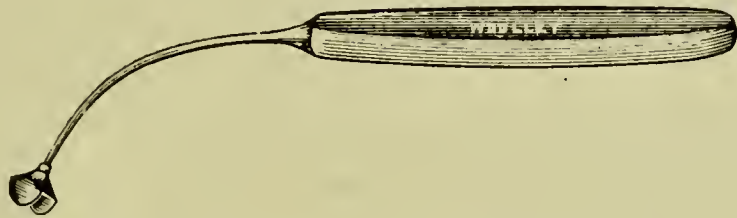


FIG. 4.—The author's "facial nerve protector."



FIG. 5.—The completed "bridge operation."

and severe vertigo, and had lasted for two or three days at a time.

On admission the following condition was noted:—The left external auditory meatus was filled by a mass of oedematous granulation tissue bathed in very foetid and sanious pus. With a probe a sequestrum was felt in the depths of the tympanic cavity. The sequestrum appeared to be partially movable, and on pressure being applied severe vertigo was produced. The temperature was 100·8°F., and the pulse 80. There was marked horizontal nystagmus. Examination with the watch showed a profound degree of deafness, and various tuning-fork tests indicated almost complete destruction of the auditory nerve. There was no optic neuritis, but slight photophobia was present. Lumbar puncture was performed, and showed an excess of a perfectly clear cerebro-spinal fluid. A complete radical mastoid operation was first performed and all granulation tissue scraped out of the depths of the cavity with a sharp Volkmann's spoon. A large fistulous opening was now found in the region of the external semi-circular canal, and on careful examination with a blunt-pointed probe a sequestrum was at once detected consisting apparently of a portion of the canal and cochlear system.

The fistulous opening was enlarged upwards and also backwards. The stapes was found to be absent and a few drops of pus were seen to be well up through the open fenestra ovalis. The fenestra was carefully enlarged with a fine bur in a direction downwards and backwards towards the fenestra rotunda.

Two sequestra were ultimately removed, one consisting of a portion of the first and second whorls of the cochlea, and the other of a portion of the superior and external semi-circular canals.

The cavity thus produced and bridged over by the Fallopian aqueduct was very carefully curetted and gently swabbed with pure carbolic acid. A strip of gauze was passed under the bridge and packed lightly into the cochlea and also into the region of the semi-circular canals. This dressing was changed every second day. After two and a half months of regular treatment the whole cavity produced at the time of operation was filled up by healthy granulation tissue, and the external wound was closed. In this way complete obliteration of both the middle and internal ears was effected. As a result of the operation there was complete disappearance of all pain and vertigo and also of all auditory sensations upon the affected side.

CASE II. T. R., male, aged 40. Had suffered for fifteen years from chronic suppurative middle ear disease upon both sides following an attack of scarlatinal diphtheria, which had also destroyed the sight of one eye. The hearing power upon the right side was seriously impaired, registering only 5 per cent. of the normal; upon the left side it was totally destroyed. The left auditory meatus was filled with pus and granulation tissue.

No view of the membrana tympani was possible. Vertigo was complained of occasionally. There was no sickness. Tinnitus was present in the right ear, absent in the left. Deep-seated pain was complained of in and behind the left ear. The patient's mental condition was dull and apathetic. The outer labyrinthine wall upon the left side was exposed as in the previous case, and an erosion found in the posterior limb of the external canal. Through this defect in the bone a bud of granulation tissue protruded.

By means of a bur the tract was opened up and the posterior part of the vestibule exposed. The cochlea was then opened, just as in the previous case, and the after treatment carried out in a similar fashion. The patient made a slow but uninterrupted recovery, a permanent retro-auricular fistula being secured.

CASE III. M. A., female, aged 21, was admitted to hospital in a semi-moribund condition, complaining of pain in the right ear and a feeling of fulness and pressure over the head. For many years she had suffered from a foul discharge from the ear. Latterly she had complained of constant dizziness and a feeling of nausea.

Upon examination the patient was found to have slight right-sided facial paresis. The hearing upon the right side was completely gone. The meatus was found full of granulation tissue, and bare bone was easily detected with a probe. There was marked horizontal nystagmus, no optic neuritis and no paralysis of the oculo-motor muscles.

A complete radical mastoid operation was first performed, and a large cholesteatoma removed. The cholesteatoma had eroded the petro-mastoid, so that when thoroughly cleared out the membranous posterior and external semi-circular canals were clearly visible. The "bridge" operation, as detailed above, was completed. The patient made a slow and uneventful recovery, slight facial paresis, however, remaining.

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INTERMITTENT LIMP.

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THERE is a condition which was described by Charcot in 1859 as intermittent claudication of arteries and which was named by Goldflam in 1895 *intermittirendes Hinken* (intermittent limp) and by Erb in 1898 *dysbasia angiosclerotica*. As the names intermittent claudication and *dysbasia angiosclerotica* both involve a preconceived theory I prefer the name intermittent limp. Although a perfectly definite affection I think it is not so generally recognized as it should be, for I believe it to be probably commoner than is usually supposed. I have seen the following five cases in the last two years.

CASE I. An officer in the army, aged 29 years, a finely built man and a great athlete, came to see me in April, 1905, and I saw him on several subsequent occasions together with my colleague, Mr. Thorburn. He went to a foreign station in 1902. He was said to have had phlebitis in the right leg in January and again in March, 1904, with œdema of the leg, pains in the calf, and "lumps" on the inner side of the knee. He came home in June, 1904, and was well for three months. He returned to his station in September, 1904, and then found that if he walked say 200 yards he had slight pains in his left leg in the calf, and at the back of his knee which at once caused him to limp, but if he rested the pain ceased. In March, 1905, similar pains also occurred in the right leg after walking. When I saw him he was complaining of much pain in the feet and calves, and both feet were cold and perfectly bloodless. His left leg was more painful than the right and in walking he kept the left ankle as rigid as possible and the knee somewhat stiff. The muscles of the legs were very well developed and firm, the knee jerks normal. No pulsation could be felt in the popliteal, posterior tibial or dorsalis pedis arteries of either side and the pulsation in the femoral arteries was weak. The radial and carotid arteries were normal, and of low tension and the heart and urine were normal. He told me that if he had had much walking during the day there was much aching in the limbs in the evening which became worse when he got into bed and lasted most of the night; but as a rule the pain and stiffness of the limbs passed away if he rested. He had never had syphilis. He was a fairly heavy smoker of strong tobacco.

The condition of course interfered very greatly with his movements so that he had to apply for a prolonged furlough. He improved somewhat while taking nitrites, but he returned to his duties and in addition engaged in many athletic pursuits although still suffering occasionally from his pains. The condition still continues and indeed seems to have again become worse for I hear he has recently again returned to England as it was impossible for him to keep on with his military duties.

CASE II. A solicitor, aged 44, was sent to see me in September, 1906. He told me that he had always been fond of taking long walks. In May, 1906, while walking he had a feeling of numbness and compression in the right foot as if he had a tight boot on; the foot then became painful as if he had a corn in the sole and it became cold. When he looked at his foot he found it was white, but while he rested the pain gradually passed away and the colour returned in red patches which slowly ran together until the natural colour returned. These attacks then came on during any lengthy walk and the pain also reached up into the calf of the right leg so that he could not proceed. After resting the pain ceased but soon returned when he resumed his walk so that he had to return home limping on his way. The attacks came on more severely if he was walking on a hard pavement. He had no pain in the left leg.

On examination I found both legs well developed and strong, the knee-jerks, urine and heart normal, but the tension of the radial artery was slightly above normal. Pulsation in the right posterior tibial and dorsalis pedis arteries was only just perceptible, but on the left side was well marked. A radiograph of the right leg showed a faint linear shadow possibly of the posterior tibial artery. He told me he smoked about thirty cigarettes a day. I saw him again about three months later but he had not improved.

CASE III. The secretary of a technical school, aged 47, came to see me in April, 1907. He was a non-smoker and was very fond of bicycling. For many months while walking he had suffered from intense pain under the right heel and for three weeks previous to his visit this pain had spread into the right foot and up the front of the shin. Some times the pain started in the centre of the dorsum of the foot and spread up into the muscles of the front of the leg. If he looked at his foot during the attack the front of it was white "like that of a corpse." The attacks came on after he had walked about 50 yards and compelled him to stop so that his "circulation in the foot could get going," the pain ceasing during the rest, only to return again a short time after his walk was resumed. The left foot never pained him. On examination his legs were

normal except that the right foot was cold and white and no pulsation could be felt in the right posterior tibial and dorsalis pedis arteries, but was present in the right popliteal artery. Pulsation in the arteries of the left side was normal. The urine and heart were normal and the radial pulse was of low tension. His condition improved by massage.

CASE IV. A wine and spirit traveller, aged 64, came to see me in May, 1907. He was a fine-looking man, very well developed and muscular, especially so in the legs, and has always been energetic and a great walker and athlete. After an attack of influenza and typhoid fever four years ago, when he was in bed for sixteen weeks, he had pains in both calves. This recovered but returned in six months. It again disappeared but returned fifteen months ago and has been present in attacks since. While he is still or walking about the house he has no symptoms. If, however, he walks outside at an ordinary speed for about 300 yards he has a numb pain like toothache or a tightness just above the left ankle and in the calf which becomes acutely tender on pressure. If he stops walking the pain almost disappears, but if he walks another 200 yards it returns with greater intensity and is more in the form of cramp and he has to drag the leg after him. He has a similar but slighter pain also in the right calf at the same time but not so much in the right ankle and foot. If he takes his boot off during the attack the left foot is found to be quite white and although it is cold to the touch he says it has a hot sensation. He has never smoked but used to take a large amount of alcohol in his business, but has not done so for some years past, and he has no alcoholic appearance.

There is a considerable amount of albumen in the urine but no sugar; he has no other symptoms of Bright's disease, and the radial pulse is of low tension. No pulsation can be felt in the arteries of the left foot, nor in the dorsalis pedis of the right side, but the right posterior tibial artery is just perceptible, but much weaker than normal. He is somewhat short of breath on exertion, but he says this has always been the case, and there is a systolic mitral murmur which from his history has probably been present many years. He obtained no relief from potassium iodide or nitroglycerine or sodium nitrite.

CASE V. A labourer, aged 50, who went to the Out Patient Department of the Manchester Royal Infirmary some weeks ago was kindly sent to see me by my colleague, Dr. Brockbank. He was a well developed man with firm and strong muscles. Physical examination revealed nothing except that there was no pulsation in the right posterior tibial and dorsalis pedis arteries, and the right foot was colder than the left. He complained that for some months after walking a short distance he

had great pains in the right foot and calf with cramps of the muscles which caused him to stop. After resting a time the pains and cramp-like feelings disappeared but again came on after walking a short distance further. There was nothing in his previous history to account for these symptoms, but he was a heavy smoker.

It will be noted that in each of the five above mentioned cases the physical signs and symptoms are practically the same. More or less suddenly a man previously healthy experiences pains in the foot, ankle and calf, together sometimes, with cramps of the muscles, which cause him to stop, and if he looks at the foot he finds it to be cold and bloodless. On resting, however, the pains gradually disappear and the colour slowly returns in red patches which ultimately run together. On resuming the walk, however, the symptoms return so that it becomes impossible for these patients to walk any distance. Physical examination reveals nothing except an absence of pulsation in the dorsalis pedis and generally also in the posterior tibial artery. The muscles are often very well developed and there is no sign of any affection of the nerves. As a rule only one leg is affected, but both may become involved. Nothnagel has related a case in which one arm was affected and the late Dr. Dreschfeld told me he had also seen an arm affected with the disease.

History. The history of this affection is very interesting. As pointed out by Osler in his lectures on angina pectoris (p. 115), Allan Burns in his "Observations on some of the more frequent and important diseases of the heart" (published in 1809), states in illustration of the view that angina pectoris is caused by atheroma of the coronary arteries that "if we call into vigorous action a limb round which we have, with a moderate degree of tightness, applied a ligature, we find that then the member can only support its action for a short time; for now its supply of energy and its expenditure do not balance each other; consequently it soon, from a deficiency of nervous influence and arterial supply, fails and sinks into a state of quiescence."

M. Bouley, Junior (*Arch. gén. de méd.* Vol. xxvii., p. 425, 1831), made some observations on what he described as inter-

mittent claudication (the first time the term is used) occurring in a mare aged six years. The attacks came on suddenly after a few minutes exercise and were caused by an obliteration of the femoral arteries. As long as the animal was in repose, the blood could arrive by the collateral vessels, but when it trotted these vessels could no longer transmit enough blood and the members were struck with numbness and deep pain.

This condition is, it seems, well known to occur in horses and is called by the French veterinary surgeons "boiterie." Charcot published a memoir on intermittent claudication in 1859 (*Mem. de la Soc. de biol; and Gaz. méd. de Paris*), and in this he gives a vivid description of the sufferings of horses affected with this malady, the symptoms being practically the same as those occurring in man.

But previously to this, Sir Benjamin Brodie in a lecture on "mortification" published in 1846, says "if you cross-examine a patient who has mortification of the toes, he will generally tell you, that for three or four years preceding, he has had occasional pains in the lower limbs; a sense of numbness in them, that his feet were liable to be cold; that when they again became warm, after having been cold, they have been very painful; and that he has had a sense of weakness of the muscles. Such patients walk a short distance very well, but when they attempt more than this the muscles seem to be unequal to the task, and they can walk no further. The muscles are not absolutely paralysed, but in a state approaching to it. The cause of all this is sufficiently obvious. The lower limbs require sometimes a larger and sometimes a smaller supply of blood. During exercise a larger supply is wanted on account of the increased action of the muscles; but the arteries being ossified or obliterated, and thus incapable of dilatation, the increased supply cannot be obtained. This state of things is not peculiar to the lower limbs. Wherever muscular structures exist, the same cause will produce the same effect. Dr. Jenner first, and Dr. Parry of Bath afterwards, published observations which were supposed to prove that the disease which is usually called angina pectoris depends on ossification of the coronary arteries." Brodie further says "when the coronary arteries are

in this condition (of ossification) they may be capable of admitting a moderate supply of blood to the muscular structure of the heart—but whenever the heart is excited to increased action—then the ossified arteries being incapable of expanding so as to let in the additional quantity of blood required, its action stops and syncope ensues; and I say, that this exactly corresponds to the sense of weakness and want of muscular power which exists in persons who have the arteries of the legs obstructed or ossified.” It will be seen that the above is an excellent description not only of intermittent limp but also of its causation.

Charcot (*Le Progrès Médical*, 1887. Vol. ii., pp. 99 and 115) again discusses the affection and mentions two fresh cases. Since then many cases have been recorded from time to time and the disease discussed in all its aspects and especially by Potain, Goldflam (who has many papers on the subject since 1895, *Deutsch. med. Woch.*, p. 36), Erb and Oppenheim; and on the pathological side by Parkes Weber, Pearce Gould and others. There is a particularly good article by Grassmann in v. Ziemssen’s *Festschrift* (*Deutsch. Arch. f. klin. Medicine*. Vol. 66, p. 100).

Ætiology. This condition is almost only found in men between the ages of 25 and 50 years. So far as can be judged from a considerable number of recorded cases neither syphilis, gout, kidney disease nor diabetes is a causal agent, although such diseases have been met with as coincidences in different cases. Nor does it generally form part of a generalized arteriosclerosis. Erb thought that excessive tobacco smoking was a strong factor in its production and although two of my cases were non-smokers it would seem very probable that tobacco may be a predisposing cause. Jews are said to be specially liable to be affected, but I have never yet seen a case in a Jew. Goldflam has found in some cases that more than one member of a family was affected, and in others he thought there was an inborn predisposition to the disease.

Course and prognosis. The condition may last for years with but little if any sign of improvement. But if care be not taken to avoid over-exertion the symptoms get worse and in not

a few cases gangrene has ensued requiring high amputation and this is one of the reasons why the disease should be recognized as early as possible.

Pathological anatomy. This affection is practically always associated with narrowing or actual obliteration of the arteries supplying the limb, and this may even extend into the smallest branches of the vessels. In some case the vessels supplying nerves were affected with some degeneration of nerve fibres, but as a rule the nerves and muscles were healthy. The change in the vessels consists of a very definite obliterative endarteritis such as will be found illustrated in the article by Michels and Parkes Weber in the Transactions of the Pathological Society of London, Vol. 56, Pt. ii., 1905. In some cases large or small calcareous masses have been found in the vessel wall; and Saenger and also Ramsay Hunt (*Medical Record*, May 27th, 1905) have been able to show the calcareous change in the artery by skiagraph.

Pathology. The history of this disease shows how closely similar it is to angina pectoris due to narrowing or obliteration of the coronary arteries. Burns in discussing angina pectoris shows how similar symptoms can be produced by a slight ligature applied to a leg which is then put into action; and Brodie gives a good description of the disease as due to obliteration of the arteries of the legs and shows how similar this is to angina pectoris. The pathology of the two affections is practically the same, and indeed intermittent limp might almost be called "angina cruris." While the limb is in repose the blood in the collateral vessels is sufficient, but as soon as the muscles are put into action and require more blood, the pain and cramp are set up and at the same time there is a lessened amount of blood in the superficial structures and the coldness and intense pallor of the limb occur. It has been assumed by some that during the attack an actual spasm of the vessels also occurs but it does not seem to me to be necessary to assume this.

Treatment. Unfortunately but little can be done in the way of treatment. Potassium iodide and nitrites are more or less useless. Possibly massage may be of service to improve

the local circulation. Certainly tobacco should be eschewed; the limb must always be kept warm and the foot never compressed by tight boots. It is very important that such over exertion as will bring on the pain should be avoided as far as possible.

The reason why I have ventured to bring forward this already well described condition is that just as Charcot said in 1887 that the disease was not sufficiently well known so I still believe it is but seldom recognized, and that considering I have seen no less than five cases in two years it must be commoner than is usually supposed.

HYPERPLASIA OF SUPERIOR MAXILLA.

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With remarks by
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THE cases which I wish to describe here illustrate a condition which is not commonly met with, but which does occur from time to time, and gives rise to serious thoughts when first seen as to its nature and as to the appropriate treatment to be adopted.

In the first place, the hyperplasia is one of bone and perhaps may be called, for descriptive purposes, a hyperostosis, to signify that the changes which occur are limited to the bone itself. The clinical aspect is more likely to come under the notice of the dentist than the surgeon, for either as a factor in its causation or as an accompaniment, we find that in the majority of these cases there is a more or less extensive caries of the teeth. It may be the slowly increasing swelling of the upper jaw, or the pain which will determine the sufferer to seek the aid of the dentist. The swelling is found to effect, primarily, both walls of the alveolus; presenting a much broader appearance than the opposite side. From thence it spreads to the outer wall of the superior maxilla. At the same time, it more or less, fills up the maxillary antrum. In no case have I found it to invade the nasal or orbital fossæ. The pain is generally referred to the distribution of the superior dental nerve when due to the pressure of the growth on the nerve trunk, or it may be limited to the exposed nerve endings in the carious teeth. In all cases, however, the pain is not of a very severe character, and differs in this respect from that due to malignant disease.

The models, from which the first illustration is taken, were taken from a case which I operated upon at the Dental Hospital

some two years ago. The patient was a servant girl, age 19, who had suffered pain and discomfort with her teeth in the posterior part of the left upper jaw (Fig. 1). As will be seen there is a smooth swelling affecting chiefly the external wall. It was hard on palpation and gave a shadow on transillumination. It also was observed to be bulging in the canine fossa above. There was no affection of the eye or nose. I made a longitudinal incision over the alveolus and found a very thin layer of compact bony tissue, which however was somewhat porous in character, and beneath this I came upon cancellous bone, very vascular, and which, with a gouge, cut with the consistency of a potato. I found that the whole of the antral cavity was filled with this material, and I removed all that was possible with the gouge as far back as the tuberosity and forward as far as the canine tooth. As the tuberosity was not much enlarged it was left. I then packed the cavity with gauze. An impression was taken in wax, and a denture to cover the opening made in the workroom of the hospital; the gauze was replaced by the plate and subsequently fresh plates were made on two occasions to accommodate the shrinkage of the tissues. She made an uninterrupted recovery and was able to dispense with the plates in eight weeks after the operation.

This patient came to me again in September of this year, nearly three years after operation, with difficulty in closing the teeth owing to swelling of the tuberosity, she had had no neuralgic pain since the operation, and only the pressure of the lower teeth on the swollen tuberosity caused pain. The other parts of the jaw had remained unaltered. I removed the tuberosity by a transverse section, after turning back the soft tissues, and found the bone to be similar in structure to that previously removed. The wound healed in three weeks.

The pathological report was kindly made for me by Dr. I. Walker Hall, now Professor of Pathology in the Bristol Medical School. In his report he says:—

“The tissue consists of well formed bony tissue. The laminae of bone are already laid down, and the bone corpuscles stain well. The interstices of the bone are occupied by a thick layer of actively proliferating osteoblasts, amongst which are



Fig. I.



Fig. III.

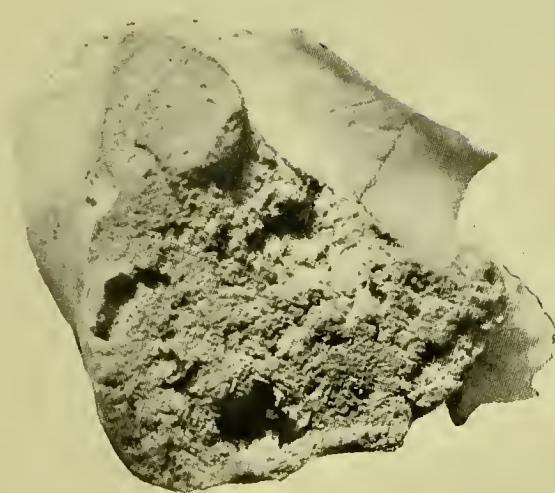


Fig. II.

Superior surface of Maxilla excised showing the antral cavity filled with cancellous bone.



Fig. IV.

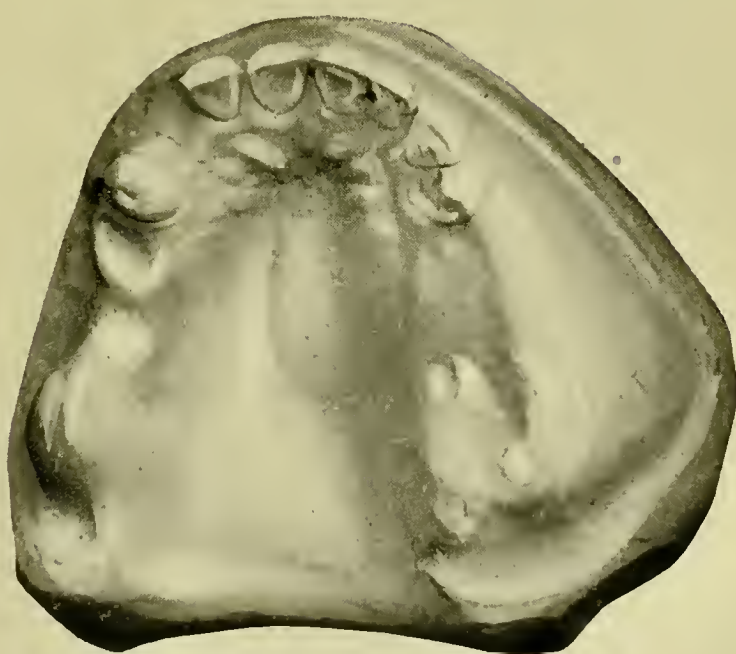


Fig. V.

a few osteoclasts. In addition, there is a rich vascular supply, and an abundance of connective tissue cells; these cells possess an unusually large amount of protoplasm. There are no collections of small cells or polynuclear leucocytes, nor are there any signs of granulomatous inflammation. The condition appears to be one of simple hyperplasia."

It will be seen from this report that the condition is benign in character and justifies the opinion that the appropriate treatment is to remove the cancellous bone as far as it extends. Excision of the upper jaw has usually been performed, and, although at once a radical and effective procedure, I believe that the less radical form of operation will be found to effect a cure.

Another case which came under my care was that of a young man, 27 years of age. He had a similar condition of swelling of the inner and outer walls of the alveolus, and two or three carious roots on the left side of the superior maxilla. He said he had noticed the swelling for eighteen months or two years, and had a constant "toothache" in the bone. The carious roots were extracted but the pain and swelling continued, and although the width of the alveolus had not apparently increased yet the canine fossa was more prominent than five months before. I opened up the alveolus and found some cancellous bone incompletely filling the antrum, but easily detected the cavity above the swelling which was smooth on the convex surface. The cavity was closed in about two months and for the past two and a half years there has been no recurrence.

The third case was that of a woman, aged 25, who had noticed the swelling in the left upper jaw for some months, and thought it to be due to a carious bicuspid tooth. The tooth having been removed the socket was found to be surrounded by spongy bone, and a steel probe could penetrate easily in all directions. There was some vascularity but nothing remarkable. The condition remained stationary for about six months, up to when I last saw her in June, 1907.

There seems to be a very scanty amount of information to be obtained on looking up the literature on the subject and, as I have had the opportunity of observing three cases, and also through the kindness of Mr. F. A. Southam, Senior Surgeon

of the Manchester Royal Infirmary, have been able to examine a beautiful dry preparation which he lent me to make a reproduction (Fig. 2. and Fig. 3). He has also arranged, for comparison a normal maxilla (Fig. 4). In this case Mr. Southam appends the following history :--

“ The patient, a girl of 19 years of age, received a blow on the left cheek 9 years before, which was followed by a slight swelling which, however, never entirely subsided. About February, 1902, the swelling slowly increased in size, and in February, 1904, when she was admitted to the Manchester Royal Infirmary the swelling had become more rapid for some weeks. Some weeks before admission, she had severe neuralgic pain in the side of the face, and it was for pain and disfigurement that she sought relief. The enlargement of the jaw appeared to be solid and hard in consistence, and opaque on transillumination. Neither the nasal fossæ, nor the orbit were encroached upon.”

Mr. Southam excised the upper jaw, leaving the orbital plate. The recovery was quite satisfactory and there has been no recurrence of the growth.

I have had the opportunity of seeing two other cases—one a relative of my own, a young lady 17 years of age whom Mr. Southam operated upon by gouging away the cancellous bone, seven or eight years ago, and in whom there has been no recurrence, the other a woman, aged 30 years, a domestic servant, sent to Mr. Southam by Dr. MacMillan, of Prestwich, who had a similar affection of the left maxilla. Fig. V. is a reproduction of the model taken of this case. She has had a steady enlargement for the past four years with occasional pain of a neuralgic character; but otherwise the inconvenience was one of disfigurement only. The swelling is chiefly encroaching upon the canine fossa below the molar process. There are three carious roots of the twelfth year molar to be seen.

From a study of these cases, I have come to the conclusion that this bony growth is simply a reversal of the process of formation of the antrum or of the absorption of bone which takes place during childhood. From some continued irritation, either from an injury, or from caries of the teeth, the bone-developing elements become unusually active; the osteoblasts rapidly in-

crease in number and form new spongy bone. The osteoclasts cannot keep pace with the increase, but are seen in microscopical sections to be accompanying the osteoblasts in all the spaces of the bone. The line of least resistance being, in most cases, the antral cavity and the two thin layers of compact bone of the alveolus, we get a slow filling up of the antrum and it is not until this cavity is filled that any serious pain or disfigurement arises.

The final condition of the superior maxilla is an exaggeration of that usually met with before the antral cavity has formed.

The age at which these cases are met with is usually between 17 and 30 years.

In all cases that I have examined only one has occurred in a man, the others being all in young women, and all being in the left maxilla.

The diagnosis from sarcoma lies in the absence of continuous pain, limitation to the maxilla, and absence of recurrence, as well as the microscopic appearances of the bone.

Should any similar cases be met with in the left maxilla, it would be as well to have an exploration made and a specimen of the bone examined microscopically before resorting to the radical operation of removal of the whole maxilla, and as these cases are not common, it would be of great interest if any such were reported upon when met with.

REMARKS BY MR. SOUTHAM.

Mr. Westmacott has so fully discussed the pathology and clinical history of this somewhat rare condition, that I have not much to add. In a fourth case which has come under my observation and not included in the preceding, the patient was also a female, and aged 25 years, but it differs from those described in the fact that the right upper jaw was affected. The enlargement had been first noticed about three years previously, and had progressed very slowly, causing no pain or inconvenience. All the teeth were absent from the affected jaw. As in the other instances, the enlargement affected the alveolar and

palatine processes of the superior maxilla, and also the lower part and anterior wall of the antrum, so that the cheek was rendered unduly prominent, and it was in consequence of the disfigurement of the face that the patient sought advice. In order to correct the deformity, the lower half of the jaw was removed. The result of the operation was very satisfactory, but the subsequent history of the case is not known.

Diagnosis. There is not as a rule much difficulty in diagnosing the nature of this condition, its slow progress, the uniform enlargement of the bone, its firm consistence, the fact that the mucous membrane retains its normal appearance, and the absence of any inflammatory phenomena, especially of tenderness upon pressure, and of freedom from pain in the early stage,—all indicating that it is not an inflammatory swelling due to periostitis, or a new growth.

In a dentigerous cyst, the swelling is more localised, and as it enlarges, a sensation of elasticity, or of “egg-shell” crackling upon pressure, can often be detected. If any doubt exists, an exploratory puncture will reveal the existence of fluid, and a radiogram may show the presence of a misplaced tooth, which is a common cause of the trouble, when a cyst of this nature has developed.

A simple or malignant epulis is hardly likely to be mistaken for this condition, nor is suppuration within the antrum, nor hydrops antri. A sarcomatous growth originating within the antrum may in the early stage be more difficult to distinguish from simple hyperplasia, but the more rapid progress of the former, its softer and more elastic consistence, often unequal in places as it increases in size, and its tendency to extend irregularly in one direction more than another instead of producing an uniform enlargement of the jaw, will usually indicate its true nature.

In hyperplasia, the condition again is very different to that met with in Leontiasis ossea, a rare affection characterised by a diffuse and irregular overgrowth of osseous tissue, springing from the bones of the face and cranium, and not infrequently originating in the upper jaw. Like the hyperplasia described, it generally commences in young adults, but differs in the fact that

the affected bone instead of being uniformly enlarged, becomes irregularly increased in size by the development of nodular protuberances of osseous tissue, which spring from its surface and project beneath the skin, causing a characteristic disfigurement of the face, hence the term applied to this affection. The condition of diffuse hyperostosis more or less rapidly spreads to the other bones of the face, and also to those of the cranium, encroaching on the different cavities, and sooner or later proving fatal from pressure effects.

Treatment. The case reported by Mr. Westmacott, and the result in one of my patients, show that in the early stage the progress of the hyperplasia may be arrested by trephining and freely removing the bone by means of a gouge. When, however, the hypertrophy is so considerable that it causes a marked deformity of the cheek, then a more extensive operation may be required and under these circumstances removal of the lower portion of the jaw gives a satisfactory result. The resulting scar is very slight, and as the orbital plate of the superior maxilla can be left, there is no subsequent deformity from falling in of the cheek, especially if a well-fitting artificial plate is afterwards worn.

ON THE ORAL, LARYNGEAL AND NASAL SYMPTOMS OF MYXŒDEMA.

By SIEGMUND MORITZ, M.D., M.R.C.P. (Lond.),

Senior Physician to the Manchester Hospital for Consumption and Diseases of the Throat and Chest; Lecturer on Laryngology and Rhinology in the Victoria University of Manchester.

THE last paper which Dreschfeld read in public was on Myxœdema;¹ a contribution to the symptomatology of this disease did therefore not seem out of place for this, his Memorial number. When I promised a paper on the laryngeal symptoms of this disease to the Editor I laboured under the mistaken idea that a myxœdematous affection of the mucous membrane of the upper respiratory tract had hitherto not at all or only rarely been observed. I was confirmed in this belief, as it was unknown to Dreschfeld, to whom not many medical facts were unknown, and as several other physicians, who had seen cases of myxœdema, were equally unacquainted with the symptoms, I am here bringing forward. The *Handbuch der Laryngologie*, by Heymann (Berlin, 1898, in 5 vols.), rightly considered the Encyclopædia of Laryngology, also mentions nothing in regard to a myxœdematous condition of the nose or larynx, and other text-books on laryngology are equally silent on this subject.

But when I came to take a more accurate survey of the literature, I found that a number of cases of myxœdema with symptoms from the nose, larynx, etc., have been described, still as they seem little known generally, I may be allowed to add the record of my case to those hitherto published:—

Some years ago I was called to see a lady, aged about 65, who complained that her tongue was getting too large for her

1. Before the newly formed Association of Hospital Physicians in London.

mouth. Unless she took great care she would bite her tongue. She had worn artificial teeth, which had been repeatedly altered, as they did not seem to fit and got in the way of the tongue; and finally, she had to give up wearing them altogether as she felt more comfortable without them. At nights he would sometimes be awakened by a choking sensation, the tongue seeming to impede her breathing.

On inspection the tongue appeared very voluminous, but there was no sign of any inflammation, no abrasion, no ulcer; it was simply and uniformly enlarged. The speech was somewhat thick, but the movements of the tongue were normal. It seemed a large and fleshy tongue, perhaps not even much larger than one occasionally meets with in cases where no complaint is made or discomfort caused.

The lady was a very stout, but otherwise healthy-looking person, and the tongue was the only source of complaint. I saw the patient two or three times within a few months and the condition remained unaltered.

Four or five years later I was called to see the same patient with Dr. Fulton, of Cheetham Hill. The patient had been ill and laid up for several months. She had, though still very stout, become very decrepit and weak. Her hair had fallen out, she was in a peculiar semi-demented condition, she would frequently pass urine under her, etc. Most troublesome was the breathing; she would sleep with her mouth open, protruding the tongue, and she complained about her nose feeling stopped up and her throat feeling tight. When asleep she would snore unmercifully, to the annoyance of everyone in the house. Her speech was thick, the voice monotonous and somewhat hoarse. The heart-sounds were weak, the urine free from albumen. The skin of the face, hands, arms and legs seemed swollen and tight, but did not pit on pressure. It was a characteristic case of myxœdema, as was also shown by the beneficial effects of thyroid gland tabloids, which brought—at least temporarily—great improvement.

The patient died several months later from increasing weakness, unfortunately no autopsy could be obtained.

Now, about the condition of the upper air passages, of which

I was able to make an exhaustive examination. The nose externally seemed normal, a large and well-formed nose. The septum normal, mucous membrane not thickened, no deviation. The mucous membrane over the lower and middle turbinals was pale and much swollen, *did not contract on painting with cocain and adrenalin*, though it felt soft to the touch of the probe. The laryngeal examination, somewhat difficult on account of the size of the tongue, revealed the mucous membrane of the pharynx swollen and thick, the uvula thick and large, but not œdematous looking. The epiglottis swollen and enlarged, pale. The coverings of both aryttænoids symmetrically swollen; the thickened interaryttænoid mucous membrane prevented the cords from closing during phonation; the cords were scarcely visible, being overlapped by the swollen ventricular bands. There also appeared to be some subglottic swelling, but with the difficulties of examination, one could not make quite certain of this. The naso-pharynx, as far as one could see it, seemed normal.

The peculiarities of this case were the early affection of the tongue, preceding other symptoms of myxœdema for years, and the extent and distinctness of the myxœdematous affection of the mucous membrane of the nose and larynx giving rise to troubles which predominated over the other symptoms of the disease.

As mentioned before, a number of cases of myxœdema, in which the nose or larynx were affected, are recorded, among the first to draw attention to these symptoms having been Sir Felix Semon, who, in a short editorial in the *Intern. Centralbl. für Laryngol.*, May, 1887, says that: "Considering the increased interest which is at present everywhere manifesting itself in myxœdema, the Editor begs to draw attention to the fact that cases of this disease may, in the first instance, come under the observation of the laryngologist or rhinologist. In the course of the last two years I have been consulted by three ladies for nasal obstruction, accumulation of mucus in the naso-pharynx and throat, a feeling as if the tongue was too large for the mouth; further, on account of the characteristic slow articulation and the leathery, dull voice. In these patients an examination showed not only a smaller or larger degree of general thickening of the mucous membrane of the upper air tract, but also that this

thickening was only a part of the general swelling characteristic of myxœdema.

Not only have the text-books on laryngology almost without exception overlooked Semon's remarks, and do not mention the condition, but the chapters on diseases of the nose and larynx in Clifford Allbutt's *System of Medicine* (vol. iv.), written by Sir Felix Semon and Dr. Watson Williams, though they give a description of the laryngeal changes seen in a case of acromegaly, do not mention, as far as I can find, those occurring in myxœdema. One of the latest treatises on diseases of the larynx, a small and excellent little book, by Harold Barwell (*Diseases of the Larynx*, London, 1907), mentions that the author had seen, "in a case of myxœdema, a smooth œdematous-looking swelling of the arytænoid and interarytænoid region; it prevented the proper approximation of the cords, and may be the explanation of the husky voice in this affection."

E. G. West (*Boston Med. Journ.*, 1884) observed in a case of myxœdema, that the lips and mucous membrane of the mouth and tongue were swollen and also the vocal cords and ventricular bands. He ascribes the sudden death of his patient to the laryngeal œdema.

In my own case, and in most others recorded, the vocal cords were found free from swelling, though Hun and Prudden (*Internat. Journ. of Med. Sciences*, 1888) mention in three cases of myxœdema which were laryngoscopically examined, a swelling of the mucous membrane and thickening of the vocal cords and their insufficient approximation during phonation. The mucous membrane of the pharynx was pale, the tongue swollen.

Farlow (*New York Med. Journ.*, 1896) describes a case of myxœdema of the throat; the tongue was swollen and thin (*sic*!) and tended to protrude. The soft palate, uvula and posterior pillars of the fauces were very much swollen, tense, thin (*sic*!), rigid, smooth, symmetrical and the two sides equally affected. The colour pale. The same condition was present on the posterior pharyngeal wall extending into the post-nasal space. The swelling did not reach much below the tip of the epiglottis. There was nothing abnormal in the larynx. The speech was slow and indistinct.

On diligent search a larger record of cases may no doubt be collected. The laryngeal and nasal symptoms of myxœdema are, I find, mentioned in some of the larger handbooks on medicine, in contradistinction to the special text-books which seem to overlook them. Thus in *Eulenburg's Encyclopædia* (2nd ed., 1888): "The mucous membrane of the mouth is simultaneously affected in myxœdema, the gums are swollen and bleed easily, the teeth become loose and fall out, the great infiltration of the tongue and palate make speech difficult, the voice becomes rough, the larynx is thickened." Thus also Gaucher in Brouardel's *Traité de Médecine*: "The mouth is kept open, the mucous membrane of the tongue, palate, gums, pharynx and larynx are affected. These alterations make speech difficult, the voice is slow, its timbre roughened." Ewald, in *Nothnagel's Handbuch* (vol. xxii., 1896), says: "The tongue is thick and voluminous, marked on its margins by impressions from the teeth, otherwise red, moist and clean. . . . In a few cases the uvula and posterior pharyngeal wall were swollen, also the arytaenoids and interarytaenoid region, as well as the ventricular bands." Kinnicut notes a chronic hypertropic rhinitis.

In Clifford Allbutt's *System of Medicine* (vol. iv., p. 470, 1897) Ord mentions the loss of timbre in the voice, its leathery character, doubtless due in part to obvious thickening of the fauces and the larynx, but still in no way resembling the character of voice observed in ordinary swellings of these parts; and further (p. 472): "The same swelling which is seen in the skin affects the mucous membrane. The inside of the lips and cheeks is tumid and is very apt to be bitten during mastication. The soft palate is generally found swollen to translucency and with great decrease of mobility. The speech is altered in so uniform a way that a diagnosis may almost be made when a patient, unseen, is heard talking. The words come very slowly and deliberately, the voice is monotonous and of a leathery timbre, no doubt much determined by the swelling of the throat, and is evidently produced with considerable effort owing to the swelling of the lips, etc.; there is probably a nervous as well as a mechanical cause for this change of speech."

In the exhaustive " Report of the Committee of the Clinical Society of London to investigate Myxœdema " (London, 1888) : In 70 cases the " throat " was once the part first affected (the tongue is not mentioned); in a total of 104 cases changes in the speech were marked in 100, in 4 they were absent; nose and smell were normal in 36, smell impaired in 11, perverted in 1, watery discharge from nose in 6 cases (in a total of 54 cases). Congestion of the vocal cords was seen in 1 out of 70 cases; no other laryngeal symptoms are mentioned. The tongue was normal in 28 cases, large, swollen and flabby in 52 (in a total of 91); the uvula and soft palate normal in 17, swollen, elongated, stiff and indurated in 31 (in a total of 48). Hæmorrhage from the throat was seen in 1, and from the nose also in 1 case.

It thus appears that nasal, pharyngeal and perhaps also laryngeal symptoms may not by any means be rare in myxœdema, and that it is desirable that all cases of this disease should be examined in this respect. It may be that not only the special symptoms are overlooked by the general physician, but also Semon's warning should be kept at heart by the specialist in the interpretation of cases similar to the one recorded. Further observations can only show whether the fact, observed in my case, that the swollen mucous membrane of the nose did not retract on the application of cocain and adrenalin can in any doubtful case be of diagnostic value. That this is probable seems likely from the pathological changes which we may assume to be present in the myxœdematous mucous membrane. The reports on the microscopic examination of such mucous membrane are sparing and of older date, so that a re-investigation seems most desirable. The changes described are an infiltration of the connective-tissue by an almost transparent or faintly granular material, separating the fibrils and increasing greatly the bulk of the connective-tissue in all its parts. This substance is a mucin-yielding modification or infiltration of the connective-tissue (Ord, in Clifford Allbutt's *System of Medicine*).

A more exhaustive description of the microscopic changes observed in the cutis from a case of myxœdema is given by Unna in Orth's *Handb. d. pathol. Anatomie*, 1894 (8th vol., pp. 1004—1010); a similar examination of myxœdematous

mucous membrane with the more recent staining methods and reagents employed by Unna would be most desirable.

According to Unna the myxœdematous cutis shows an increase of elastic and a diminution of collagenic tissue. Unna's preparations showed no cell infiltration or leucocytosis, though all parts of the cutis were a little richer in cells than normal. The cells appeared poor in protoplasm, spindle-formed and the nuclei rod-shaped, changes observed by Unna in cutis subjected to pressure.

On staining, a displacement and diminution of the collagen fibres, and an increase of elastic fibres can be observed, but both these fibres show changes from the normal in their behaviour to several stains and reagents; they have become distinctly basophile, showing, according to Unna's nomenclature, that the elastin has been converted into elacin and the collagen into collacin, a conversion, according to Unna, highly characteristic of a deep degeneration of the connective-tissue, which, according to him, is sufficient to explain its swollen and bolster-like aspect. In addition Unna observed in the swollen, succulent and quasi-œdematous papillary layer, and also in other parts of the cutis, peculiar amorphous, cloudy and also formed, crystalline infiltrations, which assume the stains characteristic for mucin.

THE SYMPTOMS DUE TO CERVICAL RIBS.

By WILLIAM THORBURN, F.R.C.S.

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Surgical Pathology, University of Manchester.*

It is peculiarly appropriate that a volume issued to commemorate the work of the late Julius Dreschfeld should contain some account of this subject, as it is indirectly due to him that attention has been prominently called to its importance. In 1903 I operated upon a case of Dreschfeld's, who first pointed out to me how little was known of the condition by neurologists and who urged me to collect and publish certain records which I had previously made. These were embodied in a paper presented to the Royal Medical and Chirurgical Society in April, 1904, and published in their transactions in the following year. On June 1st, 1904, Seiffer published in the *Neurologisches Centralblatt* a careful and complete account of nervous symptoms resembling those in my own cases and due to a cervical rib, and since then several important papers have appeared, notably in England those of Lewis Jones ("Medical Electrolgy and Radiography," September, 1906), and Hinds Howell ("Lancet," June 22nd, 1907), in America that of Keen ("American Journal of the Medical Sciences," February, 1907), and in Germany an Inaugural Dissertation of the University of Strassburg (1905) by Schönebeck. The older scattered references to the subject have been collected by the two latter authors, while Lewis Jones and Hinds Howell have confirmed and amplified my original descriptions.

It is truly remarkable how totally this by no means uncommon source of serious nervous troubles had been ignored until three years ago. Thus Keen states "I had never seen

a case of recognised cervical rib until October 20th, 1905. Within less than a month I saw four other suspected cases, of which two proved not to be cervical ribs and two others were." Lewis Jones finds that of fourteen cases which he had previously published as examples of "symmetrical atrophy of the hands in young people" ten really belong to this category. Hinds Howell has recently collected sixteen cases. Previously to my communication to the *Medico-Chirurgical Transactions* I had met with only four cases, but since then many others have been brought to my notice.* It would almost seem as if in connection with obscure affections of the brachial plexus the offending rib was to play a part similar to that of the vermiform appendix in relation to peritonitis, the same general but widely spread knowledge having, after a long period of neglect, proved suddenly to be the key to numerous difficulties.

ANATOMY.

The anatomical and morphological relationships of the rib were fully investigated by Wenzel Gruber (1869), Sir William Turner ("Journal of Anatomy and Physiology," 1870, p. 131), and Lane ("Guys Hospital Reports," 1883 and 1884), and on these matters there was little left for us to learn. More or less well developed ribs are not infrequently met with in connection with the seventh cervical vertebra, the condition being generally bilateral; in very rare cases the sixth vertebra also carries ribs and four may thus be present in one neck. Occasionally the "rib" is a mere epiphysis, articulating only with the transverse process of the vertebra, but more commonly it is a developed anterior transverse process and consists of a defined head, neck and tubercle, with or without a body. If no body be present it does not project beyond the transverse process of the vertebra, but in the more fully developed cases it extends outwards, or forwards and outwards, into the posterior triangle of the neck where it may terminate in a free end or may join the first dorsal rib, the first costal cartilage or the sternum.

Posteriorly the rib articulates in the usual manner with the body and transverse process of the seventh cervical vertebra.

* I am much indebted to Dr. Bythell for radiograms and notes of several cases with slight symptoms.



Fig. 1. Double cervical ribs from case of spinal caries with torticollis (Dr. Bythell).

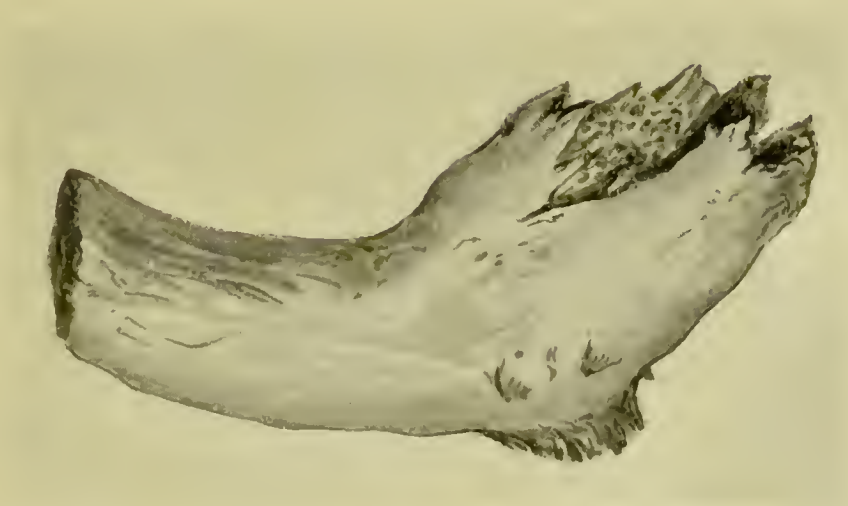


Fig. 2. Cervical rib excised from case ii. Drawn by Dr. W. E. Fothergill.

When it terminates in a free end it is bony throughout; to the first dorsal rib it may be united by dense fibrous tissue or by a joint with an articular cartilage and synovial membrane: junction with the sternum is by cartilage which unites with the first dorsal cartilage. The first dorsal rib often bears a well defined bony tubercle with which is articulated the distal end of its cervical companion.

The *shape* of the rib varies much in different cases: in some it is long, thin and pointed as shown in a radiogram given to me by Dr. Bythell (Fig. 1.); in others it is broad and flat, very closely resembling a first dorsal rib, and when thus flattened its edges are often very sharp (Fig. 2); when large enough and so placed as to lie in contact with the brachial plexus or subclavian artery it often presents on its upper border a groove for the lodgment of these structures. The *length* presents as great a variation as the shape; thus the abnormal bone may be so short as only to project slightly beyond the cervical transverse process, or it may curve round the neck, running a course of some inches before it joins the sternum or first dorsal rib. In this connection skiagrams are naturally quite misleading, as a short rib standing horizontally outwards will be very prominent, whereas a much larger bone, if flat and curved upon itself, will be comparatively inconspicuous, as shown by a comparison of the skiagram and the bone removed in case ii. (Figs. 2 and 3). Of equal importance with the size and shape of the rib is its *direction*: when running outwards it will completely avoid the nerves and vessels of the neck and will not produce clinical symptoms other than deformity; it is only when the bone curves round in the posterior triangle that it is liable to lead to trouble, and its shape and direction are thus doubtless of more importance to the clinician than its mere size. It is also important to note in operating that the posterior end of the rib lies a good deal higher in the neck than might be anticipated, the seventh cervical vertebra being only a short distance below the cricoid cartilage, while the upper margin of the sternum is on a level with the lower border of the second dorsal vertebra: thus as the patient lies with the head extended the seventh cervical

transverse process is high up in the posterior triangle. The *mobility* of the rib is also important for the surgeon and possibly in connection with the etiology of symptoms; where the bone has no anterior attachments its vertebral articulation allows fairly free movement, but when the arch is completed and there are connections with the first dorsal rib or sternum these are very strong and the bar is rigidly fixed at both ends. A condition of very complete fixation is shown in the accompanying drawing of a specimen kindly lent to me by Professor Young (Fig. 4).

The *muscular attachments* of the cervical rib are such as would be anticipated from its morphology. In well developed cases the anterior, and occasionally the middle and posterior, scalene muscles may be attached wholly or in part to the abnormal bone, and it is behind the insertion of the scalenus anticus that there will often be found a groove for the reception of the artery and plexus. An external intercostal and sometimes also an internal intercostal muscle may extend from the cervical to the first dorsal rib.

The *subclavian artery* only comes into relationship with the rib when the latter has a sufficient length and curve to reach the anterior part of the neck, but there is no absolute rule as to what this length must be, although attempts have been made to define it in centimetres. In all cases the artery, if it has any relation to the rib, passes *over* it and thus has an increase in length, the entire dome of the thorax being slightly raised by this additional bone.* The vessel is thus rendered prominent in the neck and it often presents a sharp bend where it passes over the rib; in a case of Keen's there was marked dilatation of the artery on the distal side of this bend, and in a good many other examples dilatation has been found in its vicinity. In cases in which the artery thus passes over the rib the scalenus anticus is generally attached to the latter, the vessel lying in the angle between them.

The *subclavian vein*, lying as it does much further forwards,

* In a remarkable case quoted by Schönebeck from Ehrich, in which both the sixth and seventh cervical vertebræ carried ribs the artery passed between these. Struthers, (*Journal of Anatomy*, 1874) also records a case of ribs springing from the sixth and seventh vertebræ.



Fig. 3. Double cervical rib from case ii.



Fig. 4. Seventh cervical and first dorsal ribs from specimen lent by Prof. Young. Drawn by Dr. W. E. Fothergill.

is less liable to be lifted up into the neck and is also not compressed against the scalenus anticus but can readily glide off the end of the rib whether the latter be free or be turned downwards to a fixed attachment. It is seldom if ever seen in operations and has hardly been referred to in dissections of these ribs.

The *brachial plexus*, lying behind the artery, always crosses the cervical rib in cases in which the latter does so. That the plexus may lie in a distinct groove was recognised by Gruber and Turner, while so far back as 1900 Llewellyn Phillips and Addison brought before the Anatomical Society of Great Britain and Ireland cases illustrating the passage of the nerves over a rib, which was attached at both its anterior and posterior ends. Numerous operations have also now placed beyond dispute the usual relationship of these structures, the lower trunk and inner cord of the plexus resting in more or less close contact with the abnormal bone. A much more rare arrangement obtained in a case quoted by Lewis Jones from an operation by Rawling in which a broad flat rib with a free anterior end passed between the 8th cervical and first dorsal roots, which united beyond it, the 8th cervical root being sharply kinked by the subjacent bone while the first dorsal had apparently escaped any pressure. It will, of course, be obvious that in all cases the plexus passes over the rib with a less sharp curve than is presented by the subclavian artery.

The *pleura* often extends high into the neck and is in the closest relation with the inner aspect of the rib. In such cases the cervical rib takes the place, and often the shape, of the first dorsal and determines a general raising of the dome of the thorax on the affected side.*

CLINICAL EFFECTS.

Clinically the pressure of a cervical rib may be appreciated as a source of deformity in the neck, or as giving rise to

* Possibly some of the cases described clinically as cervical ribs are in reality ill-developed first dorsal ribs, but this distinction is of morphological rather than clinical interest and will not be further referred to. It is, however, unlikely that a first dorsal rib would press upon vessels or nerves and the first dorsal nerve root ought to lie well above it.

pressure upon the brachial nerves or subclavian vessels. Bennett ("Lancet," June 8th, 1907) also reports a case in which the anterior end of a left cervical rib so pressed upon the clavicle as to cause dislocation of the sternal end of the latter, there being apparently no other inconvenience, and a similar observation is published by Schnitzler.

In some cases the rib is associated with scoliosis, torticollis or diseases of the spinal cord, but in such it can hardly be regarded as the cause of the co-existing symptoms.

Scoliosis has been frequently met with, Schönebeck having found it mentioned in 22 out of 61 collected cases, while Garré and Drehmann had previously noted the connection. Personally I have met with slight scoliosis in one case only, but Hinds Howell had one well marked and two slight examples in his 16 cases. In some of these instances it is undoubtedly quite accidental; thus in the only one which I have met with there could be no doubt that we had a slight lateral curvature of ordinary type due to inequality in the length of the lower limbs and probably to slight coxa vara.

Drehmann (quoted from Keen) has however shown that in some cases there are associated deformities of the bodies of the vertebræ, such as inequalities in the depth of the two sides or intercalated segments, and that congenital lateral curvatures are thus liable to be associated with abnormal ribs. Such conditions can, however, hardly be regarded as results of the presence of the rib and need not at present detain us. In other cases it is probable that lateral curvature is initiated by lateral deflection of the head to relieve pain, the head being approximated to the shoulder on the affected side and tension on the nerves being thereby reduced. *Torticollis* might naturally be produced by associated deformity of the vertebral bodies and was present in one of Drehmann's cases. In one of the cases communicated to me by Dr. Bythell there was marked torticollis, but this was regarded by Mr. Charles Roberts, under whose care the patient was in Pendlebury Hospital, as due to spinal caries, and the cervical rib is probably of no pathological importance although very prominent in the radiogram (Fig. 1).

Lastly the co-existence of *syringomyelia* with cervical ribs has been noticed in several cases, but these two conditions cannot be regarded as standing in the relation of cause and effect; they are either incidentally associated or due to a common developmental error in the cervical region (Schönebeck *loc. cit.* Borchardt, Berlin, klin. Wochenschrift, 1901, p. 1265, etc.).

VASCULAR SYMPTOMS.

Affections of the subclavian artery are generally manifested by changes in the radial pulse, and many of the cases in which nervous symptoms are produced the pulse will be found to be markedly weakened or even absent on the affected side, this symptom being a valuable and ready aid to diagnosis. The weakness of the pulse is not unnaturally relieved by raising the arm above the head so as to remove the sharp curve made by the artery passing over the rib, and in all my operation cases removal of the bone has removed the symptom. In the neck the subclavian artery is prominent and its pulsation, which is readily seen and felt, is often associated with a marked systolic murmur.

More serious results of pressure upon the artery have been met with. The simulation of *aneurism* by an artery raised up on a supernumerary rib has long been recognised, having been first recorded by Sir Wm. Turner (*loc. sup. cit.*) on the basis of a letter from Sir James Paget, but it is not quite certain that a true aneurism is ever produced by the presence of the rib. Dilatation has certainly been met with in several operations—generally on the distal side of the rib—but this usually subsides after operation and gives rise to no further trouble. On the other hand, Ehrich has recorded a case in which aneurism developed after operation, presumably as a result of injury to the vessel or withdrawal of support; such a condition might follow injury to the wall of any large vessel, especially in the somewhat forcible dissection required to remove a cervical rib; it presents therefore no peculiar relationship to the malformation we are considering, but it indicates the need for care in handling the vessel during operation.

Arterial thrombosis has, unlike aneurism, certainly been met

with in several cases (Keen collects ten), and *gangrene* of the tips of the fingers has been noticed seven times, but these troubles have not come within my personal experience.

The subclavian vein seldom comes into close contact with the cervical rib, and, lying in front of the scalenus anticus, is not compressed in the angle between that muscle and the bone so that venous troubles are rare, but in a few cases—including one of my own (Case vi.)—œdema has been met with. Subjective and even objective feelings of coldness in the hand are not rare, but are probably due to pressure upon nerves, with or without, anæmia from arterial pressure, and reference will be made later to this symptom.

NERVOUS SYMPTOMS.

Far more interesting than the above troubles are the *nervous symptoms* which result from cervical ribs, and it is to these that we may now more particularly turn our attention. It is in the first place clear that such symptoms are by no means present in all cases, and it is as impossible to say definitely in what proportion of cases they are present as it is to state what percentage of the population have cervical ribs. Of seventeen cases (fifteen females and two males) which have come under my personal observation thirteen presented some nervous symptoms, but such a proportion is obviously too high as it is generally only the existence of symptoms which has caused the rib to be sought for; in four cases in which no symptoms were present the condition was simply discovered by accident.

It has been argued, as in the discussion at the Royal Medical and Chirurgical Society, that in all cases the co-existence of symptoms with the rib was a mere accident and that the bony deformity could not be a cause of symptoms, but in view of the above figures, as well as of numerous collected observations, and in particular those of Lewis Jones, this position may now be regarded as untenable, especially as it is clearly proved that the removal of the rib cures the symptoms. On the other hand it must be agreed that some factor other than the mere existence of the rib is required to produce symptoms. Of these factors

the purely anatomical ones of size and direction have already been noticed but our cases enable us to indicate certain others.

All my own (13) cases, with the exception of one presenting only slight pain, have been met with in women, as have the great majority of those recorded. In nine of the thirteen they were unilateral, in four bilateral, and of the unilateral cases six presented symptoms on the right side only and three on the left side only. This selection of the right limb is moreover not due to the special prevalence of the bone on that side, as in fifteen out of seventeen cases examined the rib was bilateral; in seven of the nine with unilateral symptoms it was also bilateral; and in one bilateral case the larger rib was on the side less affected (the left). We must, therefore, conclude that there is a special tendency for symptoms to affect the right upper limb.

The age of the patients presents wide variations, the earliest date at which I have met with them being the seventeenth year (Case vii.), the latest the seventieth (Case viii.). In spite of these extremes we find, however, a very definite tendency for symptoms to appear in early middle life. Thus in eight cases in which symptoms were severe the ages of onset were 17, 20, 22, 23, 27, 35, 46 and 50; in four, which present only slight pains, the date of onset is uncertain, but the cases when seen were aged respectively 45, 50, 60 and 72; in one remarkable case paralysis was produced in the right upper limb at the age of 20 and in the left at the age of 70.*

We may then fairly conclude that symptoms are much more common in the female, that they generally involve the right upper limb and that they tend to appear in early middle life. The sexual selection is peculiar and no satisfactory explanation has been given, but it should be stated that there is no reason in any of my cases to regard it as in any way neurotic or hysterical. The age of onset has generally been regarded as bearing some relation to the completion of ossification, and it is natural to suppose that this plays an important part in the production of pressure; possibly also the little group

* Symptoms are occasionally but rarely met with in children, Keen having collected six cases between the ages of seven and fourteen.

of "senile" cases may be the result of changes in the shape or rigidity of the spine and thorax such as are usual concomitants of old age.

The special selection of the right upper limb points strongly to the more free use of the right hand as a determining cause, and it is obvious that, if the brachial plexus lies over the rib in a condition of moderate tension, the use of the limb may readily increase such tension. In this connection it may be noticed that one of my patients was a teacher of music while another was an expert pianist. The history of the evolution of symptoms in Case ii. is also striking; these first followed a wrench of the right arm; they were reinduced by a strain on getting into a train and a third time followed a fall on the right elbow; on the left side they came on in putting the arm into the sleeve of a coat. In each instance, therefore, it is probable that the shoulder was carried upwards and backwards, bringing the clavicle nearer to the rib—a mechanism similar to that which produces the typical Erb's paralysis or the "supra-brachial" type of arm paralysis. Still more suggestive of over-use of the limb as a cause of symptoms is Case ix.; in this, the only well-marked example which I have seen of symptoms confined to the left side, the rib was bilateral, but paralysis commenced at the age of 35, one month after the patient began to carry on the left arm an invalid child five years of age.

In conclusion we may say then that nervous symptoms do not occur in all cases; that they are far more common in women; that they are very rare in children; that the usual age of onset is about the 25th year, but that a second group of cases is met with in late life; that this age incidence is probably due to the completion of ossification or to senile rigidity; that the right arm is more commonly affected; and that injury or any strain plays an important part in the production of symptoms, especially when the clavicle is carried upwards and backwards.

Turning next to the nature of the symptoms we find that in nine out of thirteen cases these are purely subjective while in four only was there definite paralysis, atrophy or anæsthesia,

and it will be convenient to describe the cases as forming two groups—the *neuralgic*, in which pain and subjective weakness are alone complained of, and the *paralytic*, in which there is definite loss of power or sensation.

NEURALGIC CASES.

In the great majority of these the one prominent symptom is pain, which may be felt in the neck or in the upper limb, but is much more characteristic in the latter; in a good many of these there is also a marked feeling of weakness or uselessness of the limb, and sensations of coldness or susceptibility to cold are also common.

Pain in the neck was complained of in only three out of thirteen cases, and none of these were severe examples or indeed of well-marked type. In one it was the only symptom and may perhaps not have been due to the rib at all; in two others it was associated with pain felt vaguely about the shoulder and on the ulnar side of the forearm. On the other hand tenderness in the neck is common, and even light pressure over the projecting rib often causes a marked increase in the limb pains.

The pain in the limb is very characteristic in its distribution. Vaguely felt about the shoulder and upper arm it especially selects the ulnar border of the forearm, extending from above the inner condyle of the humerus to the styloid process of the ulna or into the fingers, and thus following the distribution of the first dorsal or first dorsal and eighth cervical roots. It is obvious that the rib must press mainly upon the lower trunk or inner cord of the plexus which is derived from these two roots, and it is fair to presume that the first dorsal lies lower than the eighth cervical, even after their union, so that the special selection of this root is readily intelligible and is moreover fully demonstrated by the paralytic cases.

In nature the pain is described as tingling, or as numb pain or as being “like the feeling caused by pressing on the funny bone.” It is often associated with a marked feeling of coldness and is apt to be aggravated by cold.

The following cases illustrate varying degrees of these

subjective symptoms as well as the local and arterial symptoms resulting from the supernumerary rib.

CASE I. Neuralgia, weakness, occasional anæsthesia; arterial symptoms. Removal of rib. Cure.

F. A., a married woman, aged 27, was sent to me in March, 1907, by Dr. Hopkinson of Withington. She stated that she had "always" suffered from feeble circulation in the hands, and had "always" noticed that the right side of the neck was a little fuller than the left. For rather less than a year she had noticed a distinct "lump" in the right posterior triangle of the neck. For a few years past she had suffered from occasional loss of sensation in the right hand, chiefly when holding small objects, and this was becoming more frequent and was accompanied by occasional tingling in the fingers "as if she had knocked the funny bone." These troubles were felt principally in the index and middle fingers, slightly in the thumb and ring finger, and not at all in the little finger. Along with these more defined subjective symptoms there was some general aching of the right arm which tired more readily than the left.

On examination both sides of the neck presented distinct hard prominences in the lower part of the posterior triangles which felt like cervical ribs. That upon the right side was distinctly larger and was tender on slight pressure. The subclavian arteries were both clearly felt and appeared to be lying free and in front of the bony prominences, but the right radial pulse was feebler than the left. No objective muscular weakness or wasting and no anæsthesia could be detected. The radiogram (Fig. 5) shows very clearly the right cervical rib, but as usual gives a very imperfect idea of the size of the latter which is so foreshortened as to appear only as a short thick projection.

The marked subjective symptoms on the right side led me to remove that rib. A straight incision in the posterior triangle near the border of the trapezius with slight division of the anterior fibres of the latter readily exposed the projecting bone at its most prominent part. By blunt dissection it was traced back towards the spine, the periosteum being left on the bone, and the soft parts, which are here loosely attached, allowing ready separation without exposure of important structures. The base of the process was then cut across with bone forceps, after which it could be elevated from its bed, being attached anteriorly by fibrous tissue only. Blunt dissection was now carried forwards, the brachial plexus and vessels being readily raised up without being in any way cleaned. The rib was roughly round in contour, and at its base had a diameter of rather less than half an inch, gradually



Fig. 5. Cervical rib on right side as seen from behind, from case v.



Fig. 6. Radiogram from behind showing cervical rib on left side (case iv.).

tapering slightly towards an apex, which was very firmly bound down by fibrous tissue to the first rib or sternum or both. Elevation now became very difficult, and as it was continued the high dome of the pleura was torn, air rushing in with a loud hiss. Under these circumstances the tip of the process was cut off and left *in situ* with its strong ligaments, the fragment removed being about two inches long. The wound was then quickly closed.

Some pain was felt in the upper part of the right chest for about two days, but on removal of the dressing no abnormal physical signs were detected nor was there at any time cough or rise of temperature. The wound healed without difficulty and the patient left the nursing home perfectly well on the thirteenth day. The nerve symptoms had disappeared and the radial pulses were of equal strength.

CASE II. Bilateral neuralgia; arterial symptoms. Removal of rib. Cure.

C. M., aged 25, a young lady, sent to me by Dr. Lord of Colwyn Bay, in April, 1907, stated that two years previously she had fallen from a bicycle wrenching her right arm, in which for two months she had sharp pain on movement. This passed away, but returned a few months later after slightly "spraining" the arm by getting into a train. Again it passed off, to return after a fall upon the right elbow, but she continued to have occasional attacks of "rheumatism" in the shoulder especially in the winter of 1906-7. About February, 1907, she had more pain in the right arm and a feeling of weakness "as if she did not want to use it." There was nothing in these symptoms to suggest the presence of a cervical rib, and the general description of intermittent pain spread over a long period was naturally not very precise, but it was clear that the suffering was at times considerable, and this combined with the slight weakness was of serious importance as the patient was by profession a pianist and teacher of music. At this first examination her case was regarded as one of neuritis, probably of traumatic origin, and under ordinary measures there followed considerable improvement for a time.

Four months later in July, 1907, Miss M. again consulted me, and stated that although there had been intermissions the pain and weakness had continued, and that a short time previously as she was putting her arm into the sleeve of a coat she felt a curious "crick" in the left shoulder, since when she had had pain similar to that previously experienced on the right side. She now had pain about both shoulders, not radiating definitely into the arms, the right arm still felt weak, there was some tingling on the backs of both hands and she had noticed a sensation of coldness in the hands, especially on the right side. The symmetry of the symptoms now first suggested

the presence of cervical ribs or at least some lesion other than traumatic neuritis.

Careful examination failed to show any atrophy, objectively definable weakness or anæsthesia of the limbs. The right radial pulse was much more feeble than the left, both subclavian arteries were prominent and a systolic bruit and thrill were present in both vessels, being well marked on the right side and slight on the left. A careful examination of the neck left the presence of supernumerary ribs quite uncertain, but there was more fulness of the left side and I suspected bilateral bony projections. Skiagrams taken for me by Drs. Bythell and Barclay placed the matter absolutely beyond doubt, both ribs being clearly seen and the left being larger although associated with symptoms of less intensity and later date (Fig. 3).

In view of the probability of increasing paralysis as well as for the relief of pain I operated on the right side on July 29th, 1907. A straight incision some three inches long was made parallel to, and about an inch in front of, the anterior border of the trapezius and carried through the superficial structures. The transverse cervical vein alone required ligature. The upper and posterior part of the offending rib was readily exposed lying high in the neck. It was cut across close to its vertebral origin but showed no mobility and ran down into the chest as an unyielding bar. The tracing of its course downwards and forwards now proved a very difficult matter, but was carried for a distance of nearly three inches by blunt dissection. The bone continued to expand, and it was clearly attached by bone or very dense fascia, so that ultimately it had to be broken away at its anterior end, any further dissection being too dangerous to be practicable. During the operation, Dr. W. P. Stocks noticed that the radial pulse was several times obliterated by traction upon the bone or by dissecting along its outer aspect, but after its removal this pulse became, and has since remained, as strong as that upon the left side. In the final stages we heard the whistling sound of air entering the pleura but this ceased immediately after the bone was removed. Wound healing was as rapid and complete as in most operations upon the neck, but was followed after some two months by the formation of an abscess, and ultimately by the discharge of a minute sequestrum.

An attack of aseptic pleurisy in the right chest followed the operation, but cleared up in a few weeks. The pain in the right arm disappeared entirely after operation.

The specimen removed in this case is most complete and very closely resembles an imperfect first dorsal rib (Fig. 2). Sickle-shaped in outline its convex border is three inches long. At its vertebral end it is half an inch wide and a quarter of an inch thick; anteriorly, where it has been broken away, it

becomes very thin but about an inch wide. Its outer surface, which was inclined slightly downwards, is as sharp as a paper knife. The skiagram naturally gives no indication of the existence of so large a structure because it there appears very foreshortened, while its thin anterior portion would be much buried and would in any case yield but little shadow.

CASE III. Neuralgia. Removal of rib. Imperfect relief of symptoms.

The following case is in many respects a highly unsatisfactory example of the condition, but illustrates the difficulties of diagnosis.

E. O., a stout and somewhat neurotic woman, sent by Dr. Cook of Askam in Furness, began to suffer at the age of 46 from pain which was vaguely described as occupying the region of the right upper limb and breast but which principally involved the inner side of the arm and forearm. The pain was described as tingling and boring but could not be localised with any precision; it was unrelieved by any medicinal treatment. The affected limb presented no trace of paralysis or anæsthesia but as movements increased pain. Just above the centre of the right clavicle was felt, under the brachial plexus, a distinct but deep-seated rounded swelling, any pressure over which was accompanied with great tenderness and increased pain in the limb. The impression given was that of an enlarged and hard lymphatic gland about the size of a hazel nut.

On November 1st, 1906, Mrs. O. was admitted to the Manchester Royal Infirmary and radiograms were taken on three separate occasions but nothing abnormal was revealed. Both subclavian arteries were somewhat prominent and the right radial pulse was very distinctly weaker than the left. A slight blowing systolic murmur was audible over the aortic area and over both subclavian arteries, and it was suspected that there might be some atheroma, although no marked symptoms were present. The swelling above the right clavicle remained unaltered as did the pain.

After three weeks of careful observation, which always failed to discover any symptoms sufficiently typical to establish a certain diagnosis, the brachial plexus and swelling were explored. A long curved incision was carried along the centre of the clavicle, thence over the acromian process and upwards and slightly backwards over the trapezius so as to allow of the reflection upwards of a flap from the lower part of the posterior triangle. The somewhat extended insertion of the trapezius was partially divided and the brachial plexus and subclavian artery exposed by the usual blunt dissection; these structures presented no abnormality and there were no enlarged glands. The swelling which had been felt through the skin was now found

to be a rounded bony process projecting almost straight forward from the side of the seventh cervical vertebra, and the nerves were cleared away from its blunt, rounded end. The process was quite immovable, as if in bony continuity with the spine, and although firmly connected with the deep muscles of the neck had no anterior connection with the first rib or sternum. Its exposure was far less satisfactory than in the operation which I have usually adopted for the removal of a rib, and the relationships of the scalene muscles were not investigated, but about three-quarters of an inch of the finger-like projection of bone was cut off and finally torn away. Wound healing was uneventful and pain was cured so far as the inner side of the upper limb was concerned, but six months later the patient still complained of pain in the deltoid region only.

In this case there can be no doubt that the cause of symptoms was a small rib pushing forwards upon the brachial plexus, and the absence of any shadow in the skiagram doubtless arose from the fact that it could only be obtained "end on" and lying beneath the transverse process. The diagnosis was, of course, further complicated by the possibility of atheroma and illustrates how readily the condition might be mistaken for an aneurism. It also appears probable that the pressure in this case was not due to the artery and nerves passing over the rib, but to the latter pushing forwards against them and thus continuing after operation to press slightly on the upper plexus.

CASE IV. Slight neuralgia; arterial symptoms.

A woman, fifty-three years of age, who had noticed a lump on the left side of the neck for many years was shown to me by Dr. Charles Melland. Through the somewhat fat tissues is clearly felt a bony prominence occupying the usual position in the left posterior triangle. The radiogram shows the supernumerary rib and its articulation with the tubercle on the first dorsal rib (Fig. 6).

The left subclavian artery is distinctly higher in the neck than that of the right side and presents visible pulsation, the left radial pulse being slightly smaller than the right; a systolic murmur is also audible above the left clavicle only. A vaguely described numbness and tingling is frequently felt in the arms and hands, but is equally present on both sides.

In each of the above cases the most prominent symptom was pain, which was, however, associated in one with weakness of the limb. In the following slight case the only symptoms complained of were the deformity of the neck and ready fatigue of the limb which often precedes more serious results.

CASE V. Case v., sent to me by Dr. Kant, of Romiley, is that of a girl, aged twenty-two, who had noticed a "small hard

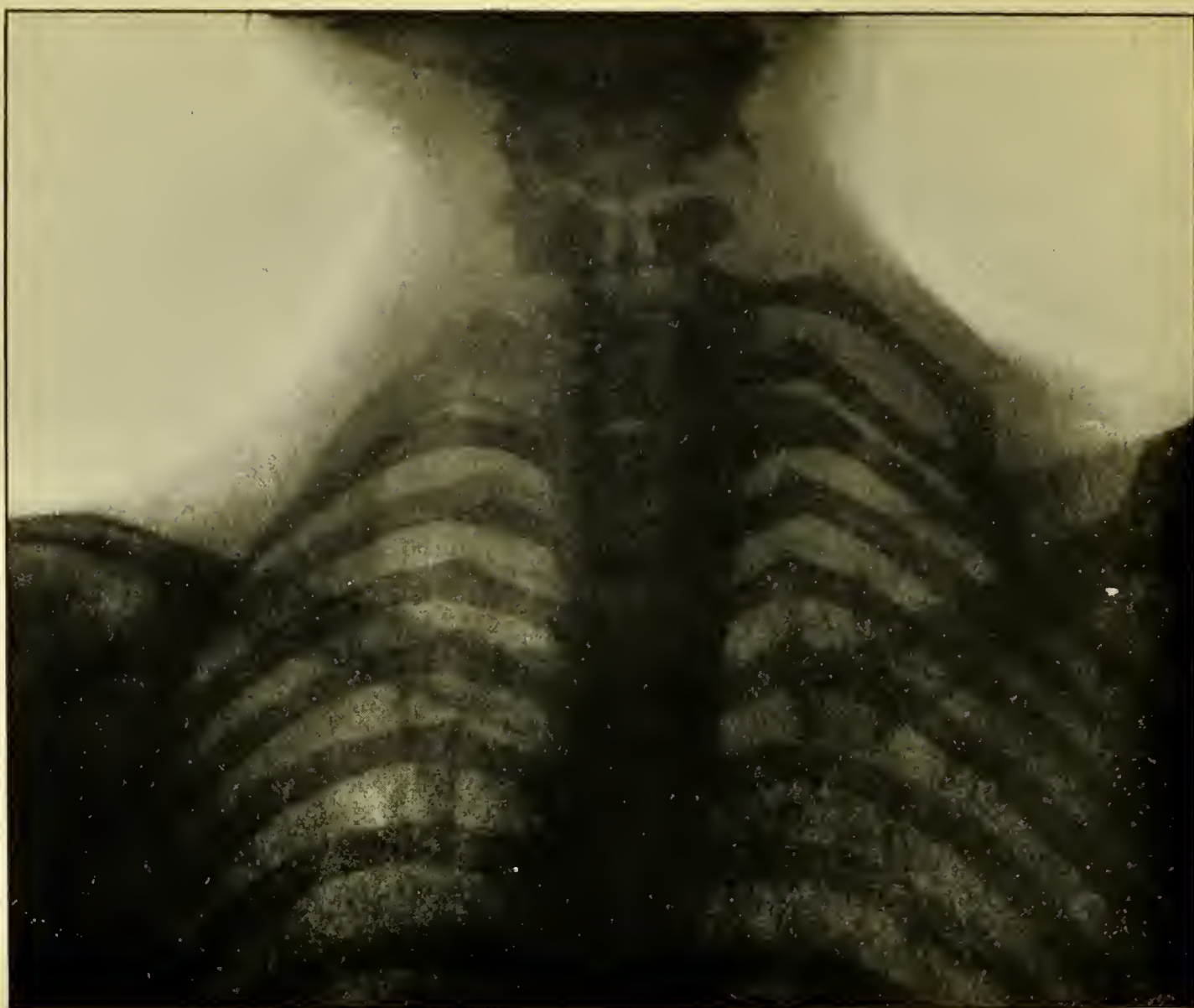


Fig. 7. Radiogram from behind showing cervical rib on right side (case v.).

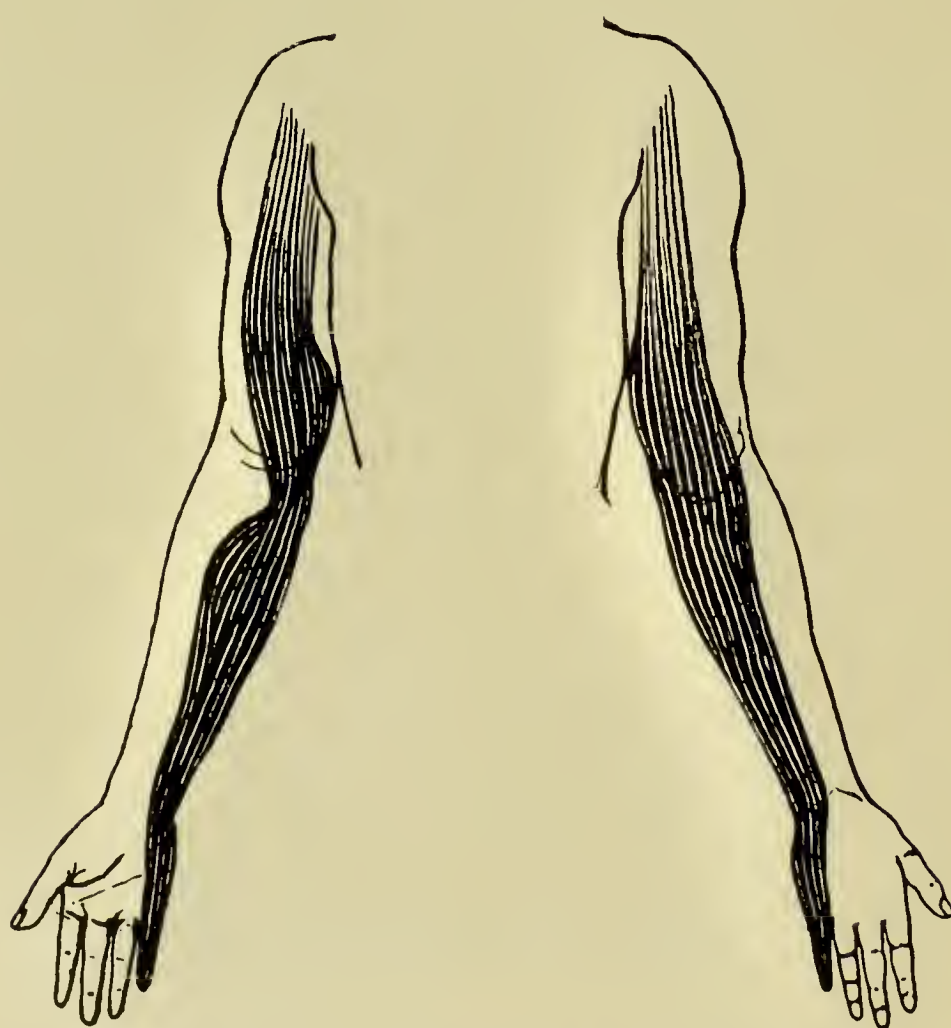


Fig. 8. Painful areas on front and back of upper limb (case vi), from photographs of areas painted by the patient.

lump" in the right side of the neck for more than a year, the lump having slowly increased in size. The neck presented obvious fulness in the right posterior triangle, and a bony mass could be clearly felt extending from the seventh cervical vertebra downwards, outwards, and then forwards. The rib is very clearly shown in the radiogram (Fig. 7) and appears to unite with the scalene tubercle on the first dorsal rib. The left side of the neck presents no deformity.

There are no pressure symptoms in this case. The subclavian artery is readily felt immediately to the inner end of the bony mass, the brachial and radial pulses being of equal volume on both sides. The only evidence of any affection of the brachial plexus is the statement that the right upper limb becomes tired very quickly.

PARALYTIC CASES.

We may now turn to the more serious cases in which we find definite objective symptoms, generally confined to irritation or paralysis of the first dorsal, or of the first dorsal and eighth cervical nerve roots. It will be found that these cases generally commence with purely subjective symptoms but that the latter tend gradually to develop into the more severe type.

CASE VI. Case vi., sent by Dr. Matthews, of Levenshulme, is that of a lady, twenty-one years of age, who had suffered from pain in the right upper limb from her twelfth year, the pain being much increased about a year before I saw her, when loss of power was also noticed in the right hand.

On each side of the neck was felt a bony prominence with the characters already described, that upon the right being distinctly the larger. These swellings were so inconspicuous as to have previously escaped the observation of the patient. The right radial pulse was distinctly weaker than the left. No radiogram was obtained.

The nervous symptoms were described with great precision by the very intelligent patient. The "grip" of the right hand was much weakened; the thumb could not be properly used, abduction, adduction, and opposition being very weak; abduction of the index finger was very feeble, adduction less markedly so; the lateral movements of the middle finger were weakened to a less extent; the ring and little fingers presented no marked weakness but were very liable to cramp, while the middle finger also became cramped on lifting small objects. Cramp was never noted in the more paralysed thumb and index finger.

Atrophy was well marked in the thenar eminence and over the abductor indicis, while there was hollowing between the index and middle fingers, but no wasting could be detected in

the intermetacarpal spaces of the ulnar side of the hand or in the hypothenar eminence. The flexor carpi ulnaris appeared to be slightly wasted, and there was a little hollowness in front of the wrist.

The location of pain was described with much accuracy, and the patient painted for me the painful area of which I was then able to take photographs, from which the accompanying diagrams have been prepared (Fig. 8). Except on the inner aspect of the upper arm, which is supplied by the second dorsal nerve, this pain was felt internally to two lines, running from the shoulder to the cleft between the little and ring fingers. Of these lines the anterior started from the tip of the acromion and ran down the centre of the biceps until within a few inches of the elbow; veering inwards it then passed internal to the tendon of the biceps, returned once more almost to the centre of the forearm and again worked gradually inwards, crossing the wrist at the line of the ulnar artery, and extending to the innermost interdigital cleft. The posterior line ran from the angle of the acromion slightly inwards to the olecranon, and thence almost straight down over the lower end of the ulna to meet its fellow in the web between the little and ring fingers.

Sensation was said to be slightly defective in the whole of the painful area and in the hand, but no objective estimation of anæsthesia was possible. The sensory defect appeared to be mainly thermal, and was noted by the patient, especially in washing. The right hand also felt cold subjectively and it presented very slight œdema.

In November of 1898, I removed the right cervical rib, and four and a half years later the patient wrote to me: "I have not felt the pain in my right arm at all since the operation. Sensation and strength in the fingers have returned slowly, and, though I am still very awkward, I am glad to say I can use my fingers much better than I could. A little while ago I could not use my first finger at the first joint, but I can do so now quite readily. With regard to the left side, I sometimes have the same dull aching pain in my arm, and the fingers of my left hand are very weak; also the muscle at the ball of the thumb is almost flat. That muscle on the right side has developed again to a great extent."

CASE VII. Case vii. was transferred to my wards by Dr. Dreschfeld. The patient is a girl aged 19, working in a water-proof manufactory, who had been troubled for two years with pain in the right upper limb. When first felt this extended from immediately above the elbow down the inner side of the forearm to the hand, but at a later date it became more diffused. Cramp and weakness of the right hand gradually supervened.

The neck presented no visible swelling, but the cervical ribs could be readily felt upon both sides, the right being the

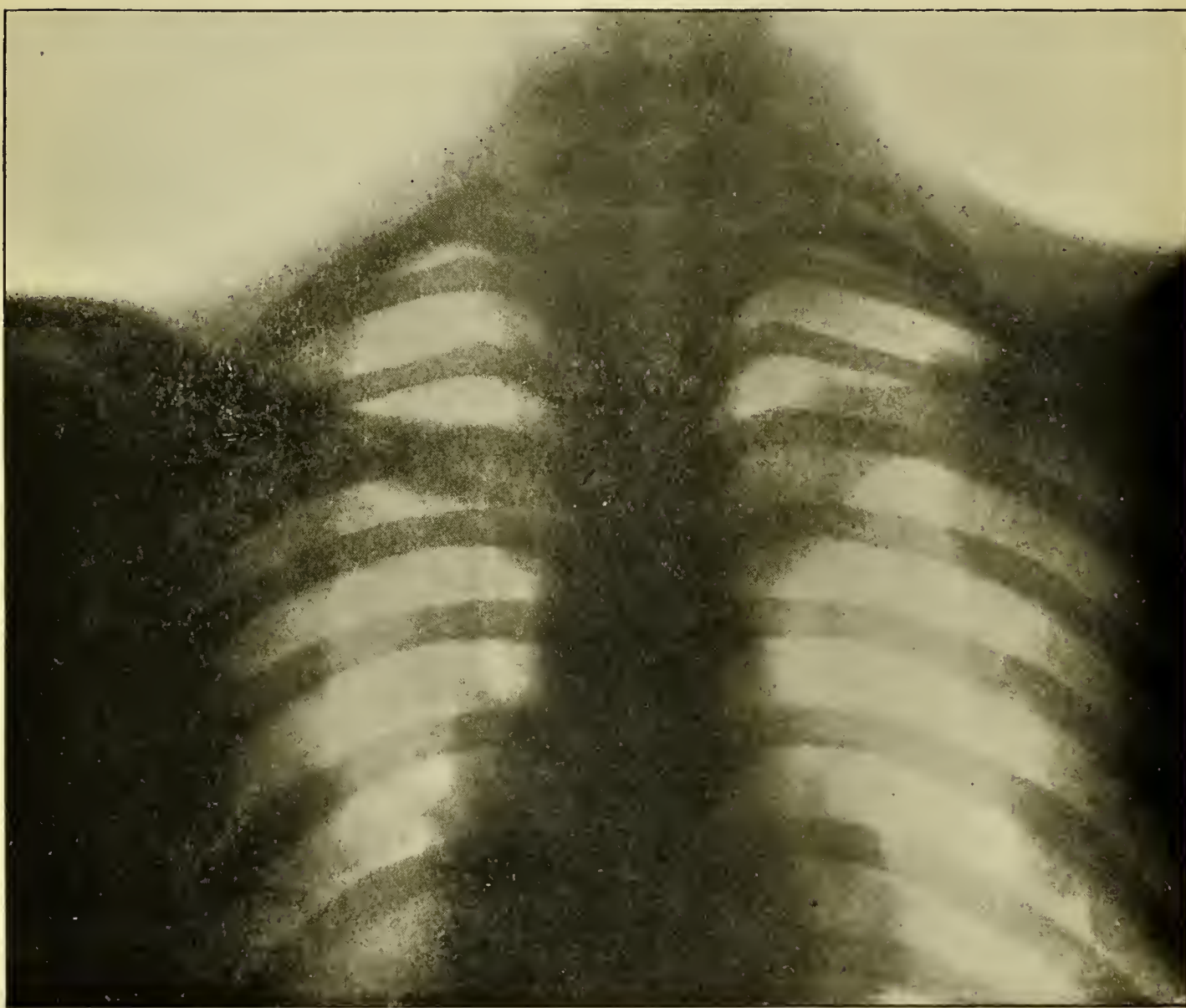


Fig. 9. Radiogram from behind showing cervical rib on right side
(case vii.)

larger. The radiogram, taken, as in other cases, from behind, is by no means clear, but indicates beyond question an excess of bone upon the right side (Fig. 9). The right subclavian artery was prominent, and the right radial pulse distinctly weaker than the left.

The right hand was very weak, the fingers being held close together and in a position of partial flexion, most marked at the interphalangeal joints. Abduction, adduction, and opposition of the thumb were all very weak, and lateral movements of the fingers were almost lost, except that slight abduction remained to the little finger. The position of flexion was more marked in the ring and little fingers than in the index and middle. Cramp was especially marked when the hand became cold, causing increased flexion, which affected principally the ring finger, and to a less extent the little and middle fingers, sparing the thumb and index. Clonic twitching also occasionally attacked the ring finger only. The constant spastic flexion of the inner fingers had given rise to a habit of straightening them out by means of the other hand. Atrophy was very marked in the thenar eminence, abductor indicis and interosseous spaces, but did not involve the hypothenar eminence. The right arm and forearm and the left upper limb presented no motor changes.

Pain and blunting of sensation were well marked, but of ill-defined outline, in an area extending from about an inch or two above the internal condyle of the humerus down the inner side of the forearm to the wrist, and thence onwards to the two inner fingers. At times this region would feel subjectively hot and burning, at other times cold and clammy.

I removed the right cervical rib, which extended well forwards into the neck, and was attached by a synovial joint to the enlarged scalene tubercle of the first dorsal rib. At the end of a year the symptoms of paralysis, spasm, and atrophy had passed away, the hand being very slightly weaker and less developed than its fellow, but slight pain was still said to be felt inside the forearm.

CASE VIII. The following case is very remarkable as showing the advanced age at which cervical ribs may first cause pressure symptoms, while it also illustrates the seriousness which these symptoms may assume and the later stages of the affection.

M. A., a widow, 72 years of age, was sent to me by Dr. Harbinson of Matlock on account of recent paralytic symptoms in the left hand, the true cause of which was strongly suspected by her medical adviser.

She stated that when about 20 years of age she began to have trouble with the right arm. This trouble was regarded as a result of confinement, and in the course of half a century much of the detail had been forgotten, but the patient remembered that for some three years she suffered from great pain in the

right upper limb, at the end of which time the pain passed away, leaving a condition of paralysis which had undergone no change for at least forty years. During the last fifteen months, *i.e.*, from about the 70th year, symptoms had commenced in the left hand, which had never before given any trouble.

The right hand was in the typical *main en griffe* position with glossy red and very dry skin. All its intrinsic muscles were much wasted, those of her thumb index and middle finger being most markedly so. Adduction and abduction of the fingers were lost as was the power of opposition, while the grip was exceedingly feeble, probably from long disuse. The sense of touch and pain was lost in the distribution of the ulnar nerve on the hand and in the little and ring fingers anteriorly and posteriorly, while partial loss extended outwards to the cleft between the index finger and thumb, and for a short distance on to the ball of the latter. (Figs. 10 and 10a.) The entire hand was of course useless, but was free from pain.

The *left hand* presented hyperextension of the metacarpophalangeal joint and flexion of the interphalangeal joints of the index finger and to a slight extent of the middle finger. Movements of abduction and adduction of the fingers and of opposition were weak, but the grip was better than on the right side, although feeble. The patient noticed that the weakness was greatest in the morning and on cold days, and that at times she was quite unable to hold any article: she had also noticed some deviation of the hand to the ulnar side. Pain was felt on the left side only, and ran down the inner side and back of the upper arm and forearm to the wrist, being located principally along the inner side of the limb in the region of the elbow joint. Sensation of touch and pain were impaired, but not lost, about the inner side of the wrist and hand. This loss extended further outwards in front than on the back of the hand. (Figs. 10 and 10a.) The left hand also gave marked subjective sensation of coldness, and cold objects when applied to its inner side felt very cold, a condition not obtaining in the right hand. As on the right side the whole of the left upper limb was feeble, but without special implication of any muscles.

Local examination of the neck revealed marked prominence of both subclavian arteries, but the left was especially well defined, and on the left side the prominence of a rib was most clearly felt, and was tender on pressure. Both radial pulses were weak, the left being more so than the right. The radiogram in this case was quite typical and showed a distinctly larger rib upon the left side, thus again illustrating the want of relationship between the size of such a rib and the severity or date of onset of nervous symptoms. (Fig. 11.)

The heart presented a well marked mitral systolic murmur and the age and general condition of the patient rendered operative treatment impracticable.

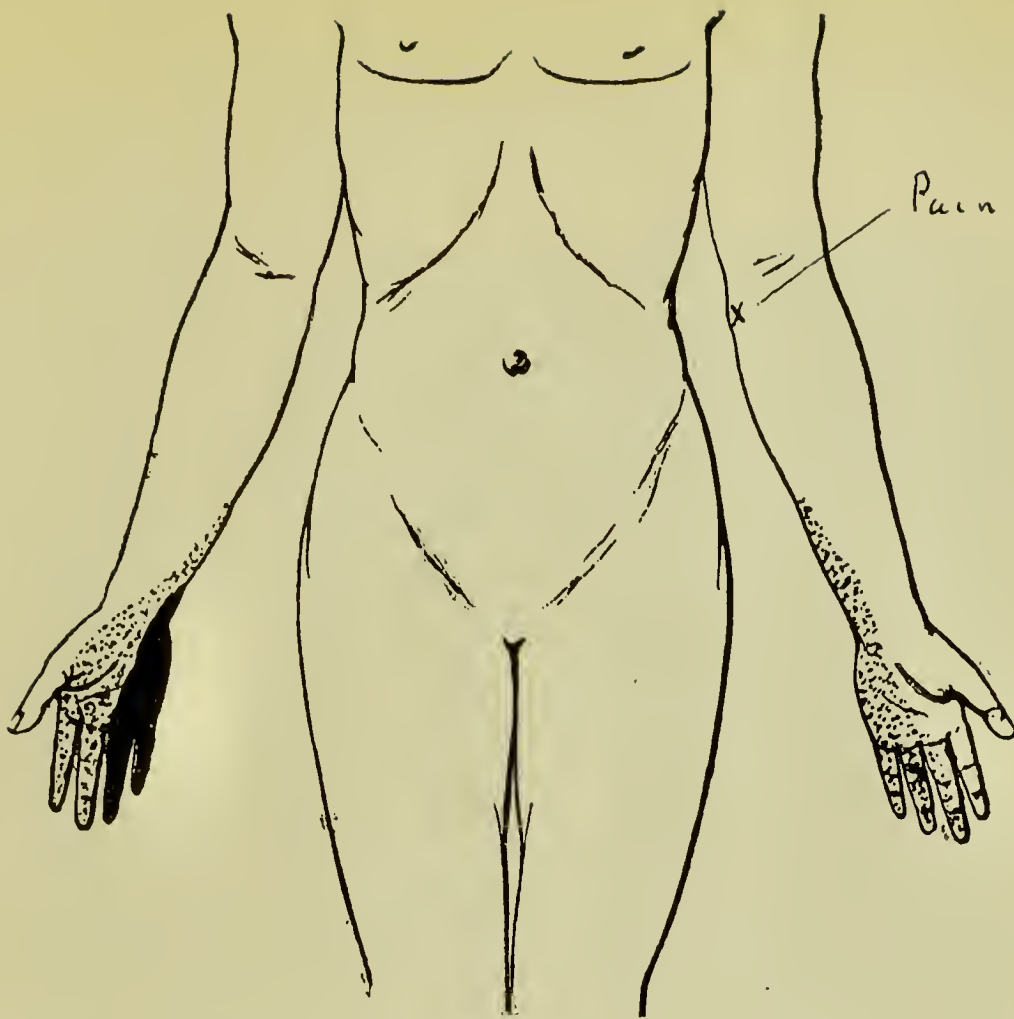


Fig. 10. Sensory disturbances in case viii. Anæsthesia shaded black, partial anæsthesia dotted.

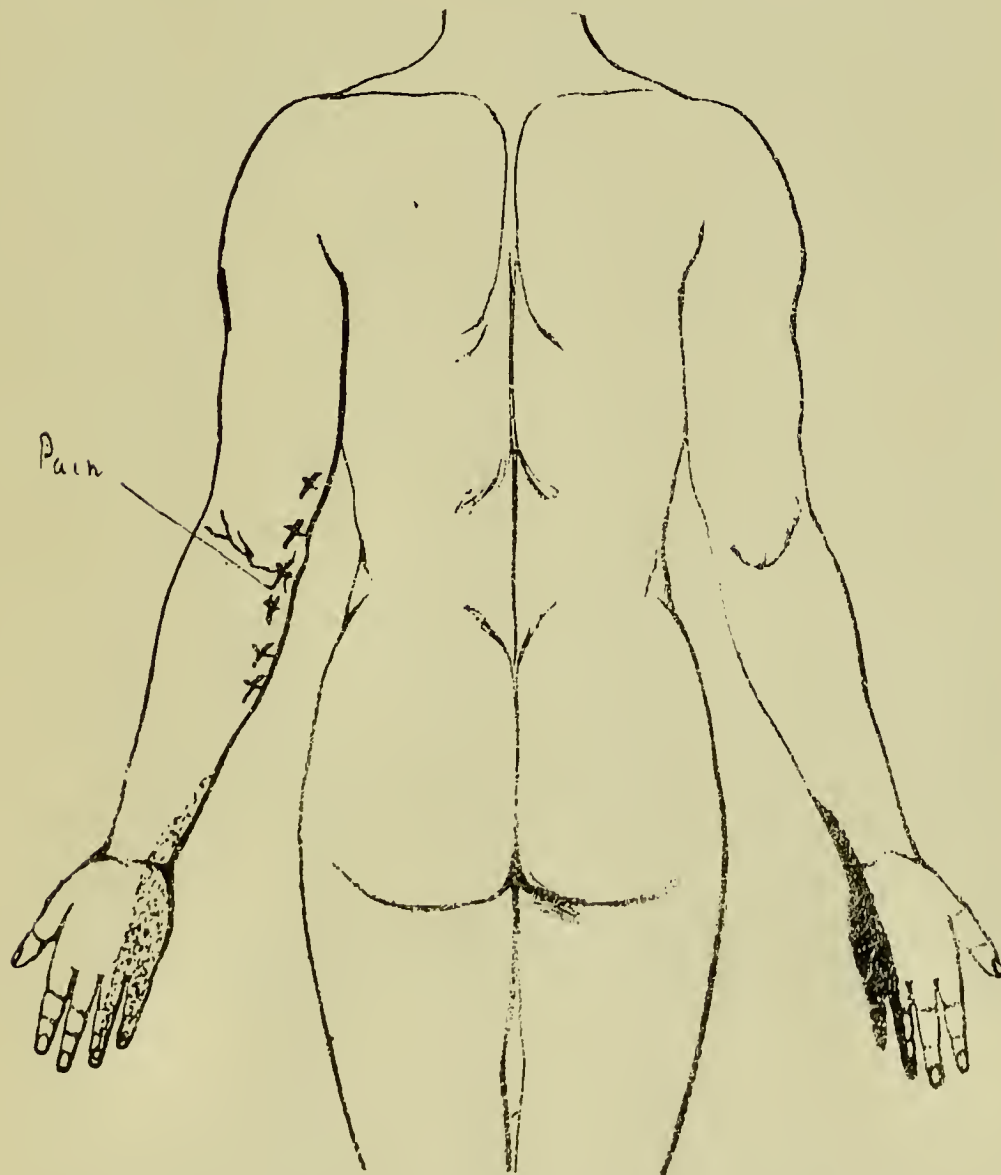


Fig. 10a. Sensory disturbances in case viii. See Fig. 10.



Fig. 11. Double cervical rib seen from behind from case viii. The original radiogram shows clearly on the left side ankylosis of the cervical rib with the first dorsal.

CASE IX. The following presents typical symptoms and is interesting in its bearing on the causation of these symptoms.

A. T., a woman aged 35, shown to me by Dr. Brockbank, had been subject from childhood to pain in the upper limbs especially on the left side: on the right this was principally on the outer side of the upper arm, on the left it involved the deltoid region and also the inner side of the forearm. For at least the last ten years no change had been noted in this condition until four months before examination, when wasting began in the left hand. On further investigation it appeared that five months ago a child, aged five years, was found to be suffering from tuberculous disease of the ankle, and the mother had acquired the habit of carrying this child on the left arm while doing her work with the right, the wasting coming on about a month later. The wasting was also said to have begun in the ball of the thumb thence spreading rapidly to the rest of the hand, quickly reaching its present height.

The left hand shows well-marked clawing of the first, second and third fingers; the little finger is straight but somewhat abducted: the palm is flat with marked loss of the thenar and hypothenar eminences and obvious wasting of the interossei. The bellies of the flexors of the fingers and of the ulnar flexor of the wrist are also distinctly wasted. All movements of the hand can be effected but are weak and difficult.

On the sensory side there is pain as already described and a sensation of coldness in the hand has been present for about a year. Sensation on the left side is blunted as compared with the right from the internal condyle of the humerus to the styloid process of the ulna, but no exact boundaries can be defined: the distinction of sharp and blunt pressure is defective, and tactile sense is apparently less impaired than pain sense. In the hand no anæsthesia could be discovered.

Both radial pulses were weak, but they presented no marked difference.

In the neck the prominence of the left cervical rib could be easily felt and was distinctly tender even on light pressure, but the subclavian arteries were not notably prominent. A radiogram shows well-defined cervical ribs on both sides, the left being the larger.*

These four cases present remarkably similar and quite typical symptoms which are of the "infra-brachial" type of brachial paralysis but have certain special characters, and it will be convenient to summarise these.

CASE VI. Pain on the inner side of the arm and forearm running into the little finger; loss of thermal sense in the painful area: paralysis of the intrinsic muscles of the hand

* See Note at end of paper.

with marked atrophy of those on its radial side and cramp on the ulnar side. Some weakness of the flexors of the fingers and wasting of the flexor carpi ulnaris.

CASE VII. Pain and slight anæsthesia with burning sensations from above the internal condyle of the humerus down the inner side of the forearm to the wrist and two inner fingers: paralysis of the muscles of the hand with *main en griffe*: atrophy of the outer muscles of the hand: cramps and twitchings of those on the inner side.

CASE VIII. On the *right* side (old-standing) paralysis and atrophy of the hand muscles; *main en griffe*: anæsthesia of the ulnar side of the hand. On the (recent) *left* side pain running down the inner side and back of the upper arm and forearm to the wrist, most severe about the inner side of the elbow joint: paralysis of the intrinsic muscles of the hand: partial anæsthesia about the ulnar side of the hand and inner fingers.

CASE IX. Pain about the shoulder and inner side of the forearm: atrophy of the hand muscles beginning in the thumb: *main en griffe*: slight anæsthesia from the inner condyle of the humerus to the styloid process of the ulnar. Wasting of the flexors of the fingers and of the flexor carpi ulnaris.

The paralysis is most marked in the muscles of the thumb, in which also it is generally first noticed, and it becomes less prominent as we pass towards the ulnar side of the hand, although it generally involves all the intrinsic muscles of the hand. Spasm on the other hand is more marked on the ulnar side of the hand, and is absent on the radial side. As in other lesions of the brachial plexus atrophy is great and, when contrasted with ordinary lesions of peripheral nerves, out of proportion to the amount of paralysis. Claw hand is of course produced in the more marked cases. In case vi. there is some weakness of the flexors of the fingers and atrophy of the flexor carpi ulnaris: in case vii. these muscles presented some spasm, and in case ix. they were also atrophied.

It is tolerably certain that the pressure upon the brachial plexus impinges upon its inner cord, which is derived from the lower trunk, and again from the eighth cervical and first dorsal roots, and it is also probable that the fibres derived from the first dorsal root lie lowest and in closest proximity to the bone, so that the clinical results will be similar to those of an affection of that root alone, although the eighth cervical may also be involved. The indications that the nerves for the radial side of the hand lie below or behind those for the ulnar side at the point of pressure, and that paralysis and atrophy thus predominate on the outer side of the hand while spasm attacks its inner side, is of considerable interest, and may prove of diagnostic value.

The sensory symptoms are also characteristic of pressure on the first dorsal and possibly the eighth cervical root. Pain and defects of sensation generally commence some little distance above the internal condyle, *i.e.*, at the lower margin of the distribution of the second dorsal root and they extend downwards to the styloid process of the ulnar or beyond into the fingers. As in other affections of the brachial plexus dissociation of various forms of sensation is noticeable. The thermal sense appears to be most readily affected and pain sense is more readily abolished than is that of touch, but no very complete or well-defined anæsthesia is found in any of the cases.

Whether this group of symptoms is to be regarded as involving solely the distribution of the first dorsal root, or whether the eighth cervical is also involved, will depend upon the ultimate answer to the question of the boundary between these two roots or segments of the spinal cord. My own observations upon spinal injuries led me to regard the first dorsal root as supplying sensory fibres only as far down the limb as the styloid process of the ulna. Head carries the root a little further on to the palm so as to include the hypothenar eminence. Kocher carries it still further on to the little finger or little and ring fingers. Thus in Kocher's scheme the first dorsal is alone involved, whereas in Head's and mine the eighth cervical would also suffer in several of these cases.

Again, my observations led me to assign to the first dorsal root the motor fibres for the intrinsic muscles of the hand only, while later observers also place in that root the nerves for the long flexors of the fingers. In several of these cases the latter are involved, but as we cannot say that the pressure is limited to the first dorsal root no light is thereby thrown upon the segmental limits. It does, however, seem probable that as the rib impinges upon the plexus after the first dorsal and eighth cervical have joined, the latter should suffer to some extent even if it lies higher and further from the bone, and hence we should expect the clinical picture in these cases to concern something more than the first dorsal segment.

Lastly it may be noted that none of these cases present any oculo-pupillary symptoms, the rami communicantes having

been given off from the first dorsal root above the point of pressure. Two cases are, however, recorded in which symptoms were present, but of these there was in one co-existent syringomyelia (Schönebeck), and Müller's appears to be the only one in which the symptoms could possibly be due to the rib.

DIAGNOSIS.

The diagnosis of the cervical rib or of complications due to its presence is generally sufficiently easy if the condition be borne in mind, but enough has been said in the early part of this paper to show that it is very often overlooked.

The *radiographic diagnosis* is of course the most important, and will usually establish the existence of the rib, regard being had to the fact already mentioned that it is by no means the most obvious bones which most readily evoke symptoms. In some few cases, however, as in our case iii., the radiographer may fail entirely to demonstrate a rib which is certainly present, and even palpable to the surgeon: in such cases the bone is probably projecting markedly forwards and its shadow is thus covered by the transverse process.

The *vascular conditions* already enumerated will prove of the greatest value as aids to diagnosis, differences in the pulse found in conjunction with nervous symptoms, being usually quite characteristic. The distinction between a prominent subclavian artery and an aneurism should not be difficult, and error is not likely to happen except from carelessness.

The diagnosis of the *nervous symptoms* on the other hand has been frequently missed, and it cannot be doubted that the most distinguished neurologists have in the past overlooked this cause of brachial neuralgia and of "symmetrical atrophy of the hands" or "radicular paralysis." The bilateral cases especially are readily mistaken for such affections as syringomyelia, progressive muscular atrophy or tumours and other pressure lesions of the spinal cord. The presence of sensory changes should at once eliminate anterior poliomyelitis in any form and the absence of oculo-pupillary symptoms or of any evidence of affection of the descending fibres of the spinal cord (exaggeration of reflexes, &c.) should suffice to exclude an

affection of the spinal cord or its coverings. Uni-radicular paralysis due to other causes can hardly, if at all, be distinguished without radiographic examination, and thus we find that in Lewis Jones' cases the great majority at least proved to be due to cervical ribs, while the cases described by Farquhar Buzzard (Brain, 1902, p. 299) and Edwin Bramwell not having been examined radiographically may possibly have been due to the same cause: they are at least so similar that in a previous communication I have ventured to quote them as probably illustrative of the condition under consideration. We may also say with safety that uniradicular paralyses due to causes other than cervical ribs are very rare and that their true pathology is unknown.

TREATMENT.

The treatment will depend upon the severity of the symptoms. In some few cases the rib may constitute a distinct deformity and removal may be desired for that reason alone, but it must be rare indeed for the deformity to be such as to render it worth removing at the expense of a scar. It must also rarely be necessary to operate on account of vascular troubles, although marked interference with the circulation and especially threatened or existing gangrene of the fingers will, as in Keen's case, call urgently for removal of the rib.

It is thus generally in connection with nervous symptoms that treatment will be sought either for neuralgic or paralytic symptoms. In the case of distinct paralysis there can seldom be a doubt as to the advisability of operating. Cases vi. and vii. illustrate sufficiently the benefits of such operation. Case viii. illustrates the disastrous result of not operating, the affected limb having remained useless for half a century. Operation will then be called for in all paralytic cases unless, as in Case viii., extreme age or the co-existence of other disease renders any surgical proceeding inadvisable.

In the neuralgic cases it is probable that relief may be given by resting the limb, avoidance of upward and backward movements of the shoulder, and ordinary methods of treatment of neuralgia. When these fail the question of operation will again arise and will be governed largely by the severity of the

symptoms. It must also be remembered that paralysis may supervene upon neuralgia very rapidly in later life, and it will therefore probably be wise to operate upon all cases of reasonable severity at an early date, and not to await the possibility of more serious nervous changes.

The operative treatment consists in removing the rib or at least so much of it as presses upon the brachial plexus and the subclavian artery. For this purpose various incisions have been used, but the majority of surgeons will probably prefer a straight and more or less vertical cut in the posterior triangle of the neck, a horizontal cut at its lower end being perhaps necessary in a very short thick neck. In Case iii. the uncertainty of diagnosis led me to adopt a curved incision turning up a flap from over the outer side of the clavicle, but this was found to be very inconvenient as not allowing dissection to the upper part of the triangle. The straight incision on the other hand gives a good exposure of the rib, but it must be commenced high in the neck as the seventh cervical vertebra lies far above the clavicle. The exact position of the incision has doubtless varied a good deal, and most surgeons appear to have made it well forward, the result being that the rib has been exposed between the artery and the nerves and the latter have been turned back. In all my cases I have made the incision further back and turned the nerves forward—operating from the side rather than from the front of the neck. The platysma is divided in line with the skin incision and it may be necessary to tie numerous small vessels, although with the more posterior incision I have had singularly little trouble with bleeding. The bone may now be sought by blunt dissection and is not always easily found as it lies deeply in the scalene muscles, and again its position in the neck may be mistaken so that it is looked for too low down. When found it is cleared by blunt dissection, but its periosteum must be removed with it as, in a case of subperiosteal resection, new bone formed after the operation, which had to be repeated. The brachial plexus must of course be carefully raised and carefully handled, as must the subclavian artery; the subclavian vein I have not seen in any case. The suprascapular nerve is somewhat in the way if the incision be posterior to the plexus, and

it must be carefully guarded. The bone being now exposed at least in part it may be cut away near to the spine and then drawn forwards. If attached in front by ligaments only it comes up into the wound very readily and can be excised with scissors, but if its anterior attachments be bony its total removal becomes very difficult on account of its relation to the pleura. In such cases it may be cut away anteriorly with gouge forceps although the surgeon will feel more comfortable after its total ablation. In any event the radial pulse should be watched and enough of the anterior part of the rib should be removed to make it certain that all pressure is removed from the artery. The method of wound-closure will depend upon the proclivities of the surgeon; personally I have not employed any drainage.

There are apparently no cases on record in which the operation proved fatal but certain definite dangers have to be encountered. In several cases there has followed paralysis of the whole or part of the brachial plexus as a result of stretching, and this has not always been transient. Reference has also been made to consecutive aneurism of the subclavian artery. If the posterior incision be used it would seem very improbable that either the vessel or the nerves should be injured, as they can be displaced forwards with extreme ease and with no trace of tension. On the other hand the pleura is perhaps more readily torn if the rib be approached from further back and in two cases I have opened its cavity; in one no trouble whatever resulted; in the other, in which we thought that only the most minute trace of air had entered, there ensued a rather severe attack of pleurisy from which, however, the patient eventually made a good recovery. In the last case the utmost care was taken and the specimen (Fig. 2) shows how it would be almost impossible to excise such a bone from its posterior end without tearing a pleural sac spread over its posterior and under surface.

In view of these personal experiences I should be inclined to continue using a posterior incision, displacing the plexus forwards, but not in future to attempt to follow to its anterior end a rib with osseous connections, merely cutting out a bridge with bone forceps and then nibbling away the anterior portion with gouge forceps. This is the more easily done as the ribs which are united by bone to the sternum or the first dorsal rib are apparently very thin in front.

NOTE.—Since the above was written case IX. has been operated upon. The rib was found to be above an inch long and projecting directly forwards so that its point impinged upon the lower part of the plexus. Pain ceased entirely from the time of recovery from the anæsthetic but there has not yet been time for improvement in muscular atrophy.

MALIGNANT DISEASE OF THE BODY OF THE UTERUS.

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The various forms of cancer of the body of the uterus and the symptoms which they produce are not very clearly described in gynæcological text books, and considerable confusion appears still to exist. For this reason I have thought it advisable to collect the cases which have come under my own observation in order that I may try to deduce some general conclusions (1) as to the symptoms, (2) as to the pathology, (3) as to the result of operative treatment, and (4) as to the differential diagnosis.

At the outset I have met with a disappointment which is not uncommon in researches of this kind, as I find that much material which might have been of value has been rendered worthless from the inadequacy or absence of notes which I thought had been preserved, or from loss of specimens which I believed were in safe keeping. But although my cases are thus much reduced in number, I think there are still sufficient remaining to justify this record, especially as the cases represent fairly well the various types of the disease.

In the first place I shall give a few notes of each case, and will then present the main points of interest in tabular form.

CASE 1. *Sarcoma of the endometrium. History.* Mrs. G., Manchester, aged 55; one confinement twenty-five years ago; menopause at fifty; four years amenorrhœa and then uterine hæmorrhage for the last twelve months. The hæmorrhage was at first moderate in amount, with irregular intervals, but gradually increased in quantity and frequency, and has been continuous for the last six weeks. It is of a deep red colour and not offensive. There has been no pain. The patient showed marked anæmia, but there had been no loss of flesh.

On June 12th, 1895, the patient was curetted, and a large quantity of soft friable tissue came away from the uterine cavity. It was then decided to remove the uterus, and vaginal hysterectomy was performed. The patient made a good recovery, and at the present date (1908) is in excellent health.

Pathology. The uterus was slightly bigger than normal. The cavity was enlarged, and contained a considerable amount of soft tissue similar to that which had been brought away by the curette. The greater portion of the endometrium had the same characters, and there was a fair line of demarcation to be seen by the naked eye between this and the muscular tissue. Dr. Fothergill kindly made a section of the tissue for me, and has described its microscopic characters in a paper which he published in "The Scottish Medical and Surgical Journal" for February, 1898. He says that "the tissue proved to be a round celled sarcoma. The sections contain very numerous small round cells, but there are also in parts many very large round and oval cells. These sections strongly resemble sections of decidua so far as the component cells are concerned, though they contain none of the uterine glands and well-formed blood vessels which are seen in uterine mucosa during pregnancy. . . . Here, then, we have a case like those mentioned by Kanthack, Eden, and others, in which large cells closely resembling decidual cells, occur in sarcomata in no way connected with pregnancy."

CASE 2. *Sarcoma of the body of the uterus.* *History.* Mrs. L., Southport, aged 50; three children, the youngest being sixteen; no definite climacteric; had irregular menstruation with intervals of two and three months about two years ago. Eighteen months ago she began to have attacks of menorrhagia. These have become much more severe and prolonged, and latterly there has been a constant discharge, sometimes sanguineous and sometimes watery and often offensive. There has been pain in the abdomen and back for some months and latterly it has been paroxysmal and acute.

On examination, a hard tumour was felt in the abdomen reaching nearly to the level of the umbilicus. On vaginal examination the external os uteri was found to be dilated to the size of a five-shilling piece. Its margins were tensely stretched by a tumour which presented. There was free hæmorrhage on examination.

On April 5th, 1899, an effort was made to remove the tumour, which was then thought to be a fibroid, through the os uteri, but it broke down so rapidly that this was found to be impossible, and as the hæmorrhage was most profuse, vaginal hysterectomy was decided on. The uterus and tumour were removed *morcellement* as rapidly as possible, the broad ligaments being clamped with forceps as they came into sight. The patient made a good recovery, and for some months afterwards her condition was quite satisfactory. About a year after the operation, however, she began to have severe abdominal and pelvic pain, and on examination it was found that there was a

hard mass in the lower part of the abdomen on the left side. This increased steadily, and she died in October, 1900.

Pathology. As the uterus was broken up on removal it was impossible to get a clear idea of its exact size and shape. Under the microscope it was found to be composed in parts of fibrous tissue but large portions were made up of large round cells and spindle cells.

CASE 3. *Glandular carcinoma.* Mrs. D., aged 67, was sent to see me in February, 1902, by Dr. Heywood of Irlams-o'-th'-Height. She had passed the climacteric more than twenty years ago, and for the last six months had been suffering from uterine hæmorrhage which became more and more profuse. The hæmorrhage was quite inoffensive; there was no pain, and although the patient was anæmic, there was no cachexia and no wasting. On vaginal examination the vagina and cervix showed the usual senile change, but hæmorrhage was seen coming from the external os. The patient was admitted to a nursing home, and a preliminary curetting on Feb. 28th, 1902, brought away a fairly large quantity of glandular friable tissue. Vaginal hysterectomy was then performed. The patient made a good recovery, and was last heard of about two years after the operation as being in good health. Since then I have been unable to trace her.

Pathology. The uterus was not much enlarged, but the cavity was dilated, and contained a friable growth which was diffused and seemed to dip into muscular tissue at one portion of the posterior wall. On microscopic examination the growth proved to be a glandular carcinoma.

CASE 4. *Glandular carcinoma.* Mrs. G., aged 52, was admitted to St. Mary's Hospital in March, 1904. She was married, but had no children. The notes of her case are somewhat vague, the only symptom noted as of importance is that there had been uterine hæmorrhage for about a year. The uterus was considerably enlarged and was removed by abdominal hysterectomy on March 23rd. She made a good recovery, but recurrence seems to have been rapid, and she died on Sept. 18th of the same year, or about six months after the operation.

Pathology. The naked eye specimen shows the uterus to be irregularly lobulated and enlarged to more than twice the normal size. There is a friable growth which is attached to the surface of the uterine cavity throughout, with the exception of the lower fourth. Under the microscope, the growth was shown to be an adeno-carcinoma. There were masses of epithelial cells which penetrated irregularly into the muscular wall. On the surface there were branching processes covered with epithelium, derived from the glands.

CASE 5. *Glandular carcinoma.* Mrs. J., aged 54, was admitted to St. Mary's Hospital on April 9th, 1904. She had one



Fig. 1, Case 5.—This photograph shows the presence of enormous masses of tumour growths in the wall of the uterus and the almost complete disappearance of the muscular tissue, which has been reduced to a meshwork amongst these masses.



Fig. 2, Case 8.—Adeno-carcinoma of villous type. Diffuse growth.

child thirteen years ago. There is no note as to whether there had been any definite menopause, but it is stated that she suffered from irregular hæmorrhage for seven years, that there had been almost constant hæmorrhage for five years, and that there was at times an offensive watery discharge. There was no pain except when large clots were passed. The uterus was removed by a vaginal hysterectomy on the 9th of April, and the patient died within forty-eight hours, apparently from exhaustion.

Pathology. The uterus is enlarged to three times the normal size and is fairly regular in outline; the walls are occupied by a diffuse growth, and the uterine tissue throughout is of a stony hardness. Under the microscope, the appearances were those of glandular carcinoma; on the surface there was excessive gland formation, while in the deeper layers there were numerous spaces packed with epithelial cells. The cancer cells in some areas had almost entirely replaced the muscular tissue (fig. 1).

CASE 6. *Glandular carcinoma.* Mrs. M., aged 51, was admitted to St. Mary's Hospital on Jan. 15th, 1905. She had one confinement twenty years ago. There is no note as to the occurrence of the climacteric. There had been a blood-stained discharge more or less continuous for nine months, and for four months this had been offensive. The patient had complained of more or less constant pain in the hypogastrium for nine months. The uterus was removed by vaginal hysterectomy on the 17th Jan., and the patient made a good recovery. She died on the 19th August, 1906, or more than eighteen months after the operation. There are no particulars as to the cause of death.

Pathology. The uterus is only slightly larger than normal. The walls are not much thickened but there is a friable growth, which dips deeply into muscular tissue and is so diffused that it involves practically the whole of the endometrium. Under the microscope, an advanced stage of adeno-carcinoma was found. Here and there gland structure was found, but there were numerous masses of epithelial cells, frequently wedge-shaped which penetrated into normal tissues.

CASE 7. *Glandular carcinoma.* Miss R., aged 49, was sent to me in November, 1904, by Dr. Nelson of Glossop, on account of continuous uterine hæmorrhage. The periods had been regular until she was about forty-seven, then there had been a year during which were intervals of three or four months between the periods; after this there was regular hæmorrhage every month until about six months before I saw her, when the hæmorrhage began to increase, both in amount and in duration. On bi-manual examination the uterus seemed fairly normal; curetting was performed, and the scrapings examined,

but the result was not decisive, as the section merely showed increased glandular tissue. The patient was better for a month or so, and then the hæmorrhage returned and gradually became as bad as before. The patient was readmitted to a nursing home in April, 1905, and the uterus was removed by vaginal hysterectomy. Convalescence was smooth, and the patient is still in good health.

Pathology. The uterus is practically normal in size. The whole of the lining membrane is covered with a diffuse growth with the exception of the lower fourth of the uterine cavity, which is free. On microscopic examination, there was found excessive and irregular glandular formation with hardly any intervening tissue. The glands are small but many of them are lined with two or more layers of cells which are larger than normal. The growth was an adeno-carcinoma in a fairly early stage.

CASE 8. *Glandular carcinoma.* Mrs. P., aged 51, was admitted to St. Mary's Hospital on Sept. 25th, 1905. She had nine children, and the last confinement was thirteen years ago. She complained of continuous uterine hæmorrhage from February to September, and the discharge had recently become offensive. For four years previous to the onset of this hæmorrhage, the periods had been absent. During the last two months she had suffered from occasional pain in the hypogastrium. The uterus was removed by vaginal hysterectomy on Sept. 27th, and the patient made a good recovery. A letter was received in September last to say she was still in good health.

Pathology. The uterus is slightly larger than normal; in sections a curious tufted growth was seen to be diffused over nearly the whole of the surface of the cavity (see fig. 2). On microscopic examination this is found to consist of branching papillary structures which are lined with epithelium which is somewhat irregular. Nearer the muscle there are solid masses of epithelial cells. The case was one of adeno-carcinoma, fairly advanced (see fig. 3).

CASE 9. *Glandular carcinoma.* Mrs. M., Bolton, came to see me early in 1906 on account of uterine hæmorrhage. She was aged sixty-three, and had been a widow for about seven years. The menopause began about 14 years ago. She had six children, the youngest of whom was twenty-one. The hæmorrhage was of recent occurrence, was not great in amount, but occurred at frequent intervals. There were absolutely no other symptoms. I saw her at intervals during the summer, and as the hæmorrhage was gradually increasing, I advised curetting for diagnostic purposes. The microscopic section of the scrapings showed adenoma of a suspicious character. The curetting had no effect on the hæmorrhage, and hysterectomy

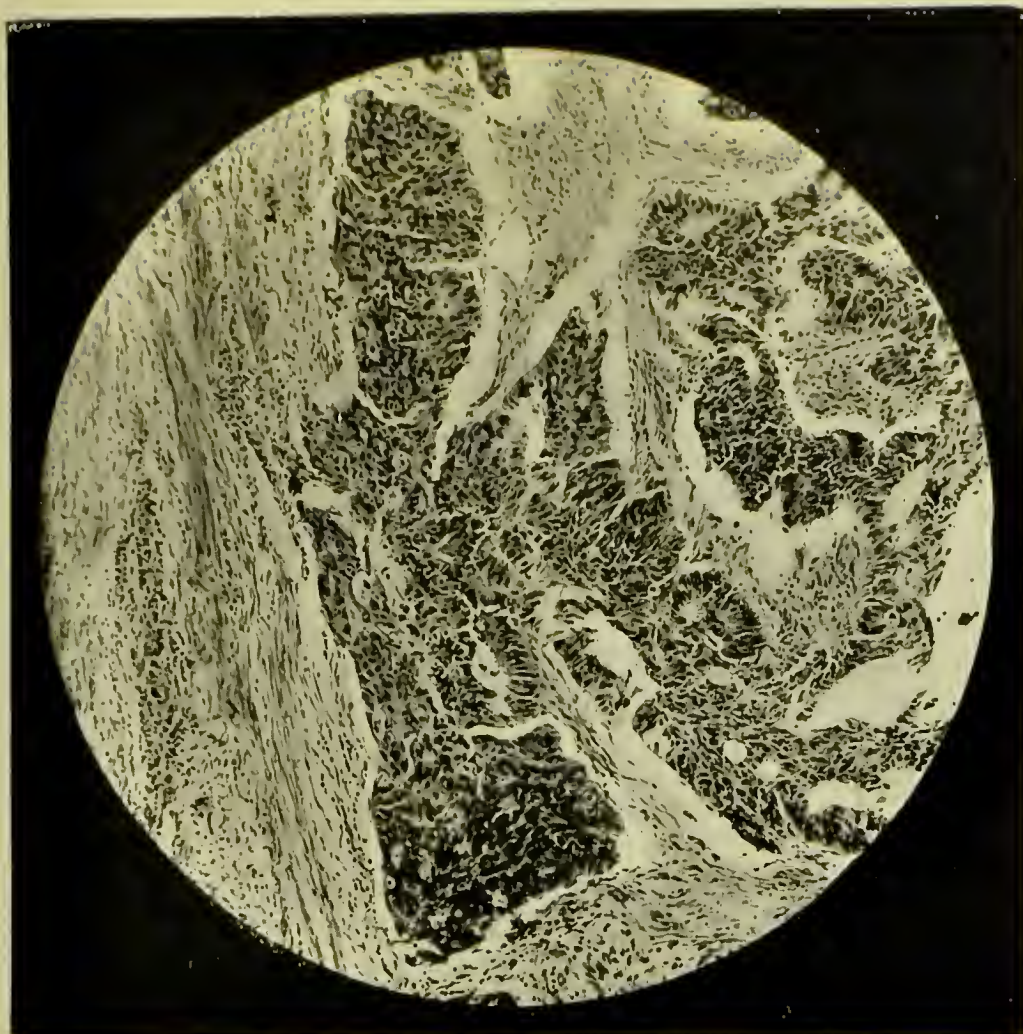


Fig. 3, Case 8.—At the right side of the photograph are situated the surface formations of this tumour, which show the structure of a columnar-celled carcinoma arranged in form of glandular acini. Deeper than this the tumour has the structure of solid masses of cells in which there remains hardly any trace of the glandular structure. These masses are situated close to the muscular layer.



Fig. 4, Case 9.—Adeno-carcinoma of colloid type. Localised growth.

was performed on Nov. 11th, 1906. The patient made a good recovery, and is now in excellent health.

Pathology. The uterus is not much enlarged, but the cavity contained a polypoid growth about the size of a small walnut, which was attached by a broad base to the fundus and posterior wall (see fig. 4). This growth was very friable in the fresh state. Under the microscope it showed numerous irregular spaces lined with epithelium. The whole section of any part of the tumour showed the same change. In the lumen of many of the acini there was a collection of cellular debris in various stages of colloid change

CASE 10. *Glandular carcinoma with change into squamous epithelioma.* Mrs. H., married, aged 66 years, was admitted to St. Mary's Hospital on May 17th, 1907. She had one child thirty-eight years ago. Her menopause appeared twenty-seven years ago when she was thirty-nine, and for sixteen years there was no menstruation. Eleven years ago hæmorrhage began, and has continued at irregular intervals to the present time; the intervals have never been longer than two months, and at times have been only two weeks. Since the beginning of the year the hæmorrhage has been profuse, and in the intervals there has been a thin, watery discharge which is not offensive. The patient was very anæmic but had not lost flesh. Vaginal hysterectomy was performed on May 18th, 1907, and the patient made a good recovery.

Pathology. The uterus is regular in outline and nearly twice the size of a normal uterus. The cavity contains an irregular friable growth which is attached over about three-fourths of the uterine cavity. This growth is found to dip into the uterine tissues in an irregular way. Under the microscope cylinders of cells closely packed are found to dip in amongst the normal tissues. As the origin of these cells was somewhat doubtful, the specimen was referred to Professor Lorrain Smith, who reports as follows: The surface growth is undoubtedly adenocarcinoma, but in the muscular wall where the tumour has invaded, the cells are becoming very like squamous epithelial cells,—a transformation that has been described by others."

CASE 11. *Glandular carcinoma.* Mrs. R., widow, 67 years of age, was admitted to St. Mary's Hospital on Oct. 7th 1907. She had two children, the last confinement being twenty-two years ago; the menopause came on sixteen years ago; twelve months ago she began to have a slight hæmorrhagic discharge, and this occurred at intervals of about a week until her admission. The hæmorrhage was never very profuse, but is gradually increasing in amount and is rather offensive; there is no particular pain. Vaginal hysterectomy was performed on Oct. 9th, and the patient made a good recovery.

Pathology. The uterus is enlarged (half as much again as the normal uterus) and is hard, nodular, and friable. An irregular growth fills the cavity, and seems to spring from a broad surface on the posterior wall of the uterus. Under the microscope the appearances were typical of adeno-carcinoma. There was much infiltration of the deeper tissues with epithelial cells.

Comparative frequency of cancer of the body and cancer of the cervix of the uterus. Cancer of the body is generally estimated as forming about 6 % of all cases of uterine cancer, and some observers put the ratio as even higher. A rough estimate of my own cases shows that this ratio is too high as far as my experience goes. I find that I have performed hysterectomy for cancer of the cervix just about one hundred times. If I allow for cases of cancer of the body which I have omitted from my list, owing to the records being incomplete, and if I exclude cases of sarcoma of the uterus, I find I have operated about fourteen times for cancer of the body. It must be remembered, however, that all, or nearly all the cases of cancer of the body are operated on; the disease is slowly progressive, and even at a late stage, when the nature of the trouble can no longer be overlooked, hysterectomy can usually be performed. On the other hand, the cases of cancer of the cervix in which operation is justifiable, form only a small proportion of the total cases. I have not investigated carefully all my out-patient and private records in order to find the exact number of cases of cancer of the cervix that have come under my observation, but I have sufficient data to enable me to state that I have seen about five hundred cases. Therefore as far as my own experience goes, cancer of the body forms only about 4 % of all cases of uterine cancer.

Age and social condition. The youngest of my patients was forty-nine, while the two eldest were both sixty-seven; four patients were between fifty and sixty, and four were over sixty. It is sometimes stated that cancer of the body of the uterus is most common in elderly spinsters or in women who have had no children, but the cases that have come under my observation do not corroborate this statement. Of the patients with uterine cancer only one was unmarried; five were married, and three were widows. Of the eight patients who were, or had been, married, only one was nulliparous.

Pathology. In two cases the disease was sarcoma. In one



Fig. 5. Case 10A.—This photograph shows the surface layer of the tumour in the form of a typical cylindrical-celled carcinoma.



Fig. 6, Case 10B.—This photograph shows the masses of tumour growth in the muscular wall. The cells are columnar in form, but there is little of the gland-like arrangement. They are in solid masses. In the midst of some of the larger masses are seen areas of necrosed cells, etc., represented by glandular débris.

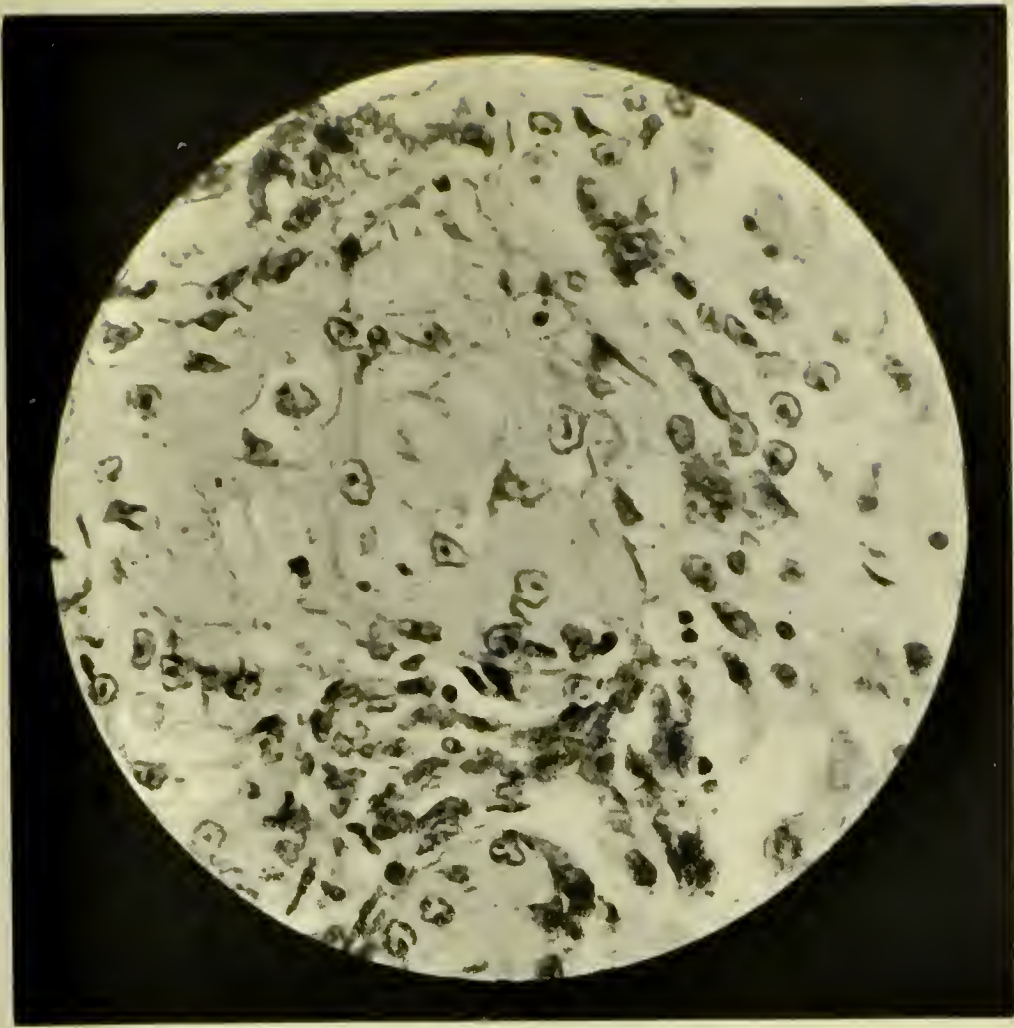


Fig. 7, Case 10c.—This photograph with the D lens shows the transformation of the tall columnar cells into rounded hyaline cells similar to those met with in squamous epithelioma. The nucleus is centrally placed in these cells and is gradually disappearing with the progress of the hyaline change.

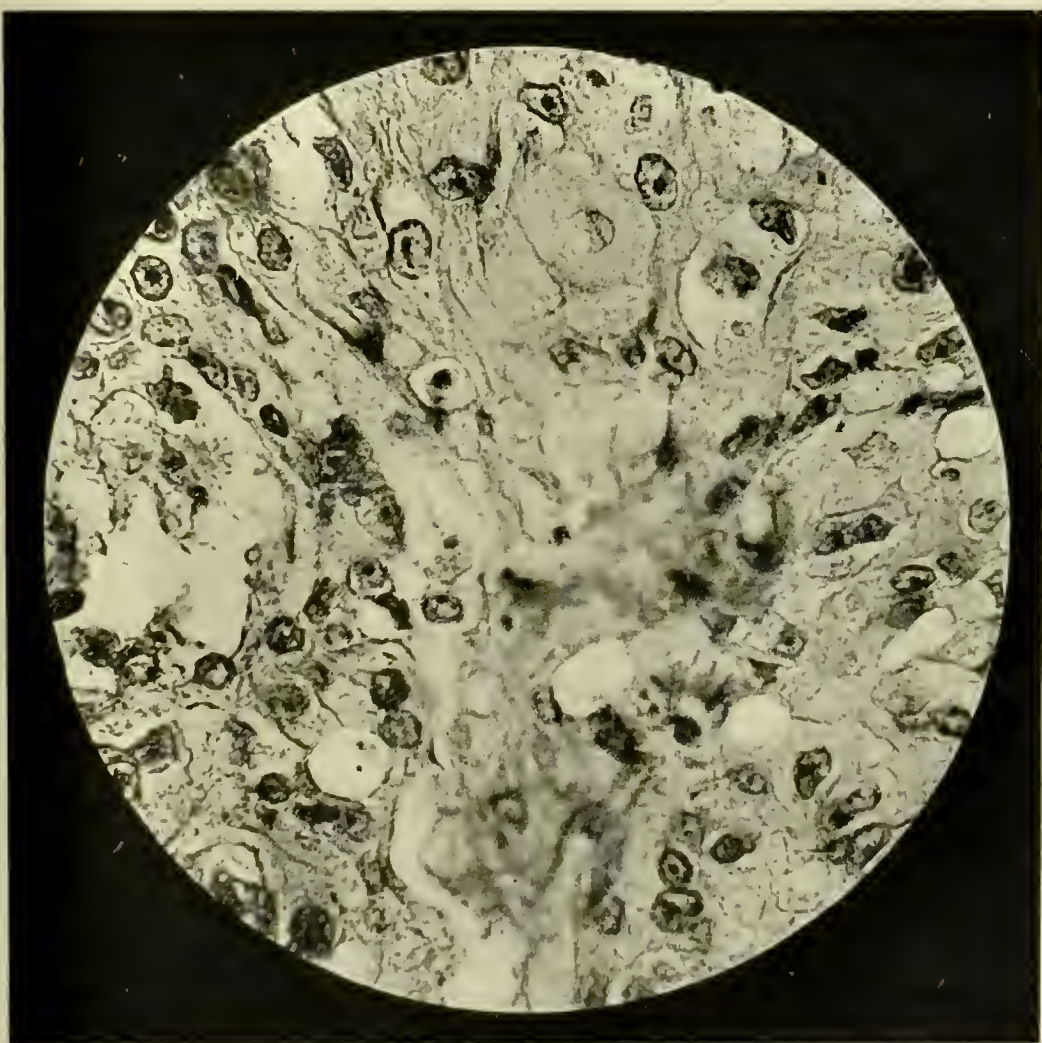


Fig. 8, Case 10D.—This photograph shows the cancer cells undergoing hyaline transformation as they appear under the 1/12 oil immersion lens.

of these (No. 1) there was a round celled sarcoma with cells resembling decidual cells limited almost entirely to the endometrium; in the other (case 2) there was a large tumour which showed fibroid structure invaded by small round cells. Whether this was an instance of the change from fibroid to sarcomatous growth, which appears to have been proved to occur, or whether it was merely an invasion of a fibroid tumour by a sarcoma originating elsewhere is doubtful.

The other cases were adeno-carcinoma in various stages. I have not attempted to draw a line between malignant adenoma and glandular cancer of the uterus. It seems to me important to avoid a multiplication of terms except when it is absolutely necessary for clearness. There seems to be no doubt that the difference between malignant adenoma and adeno-carcinoma is merely one of degree; most of my specimens show the transition very well (see figs. 3, 5 and 6). On the surface towards the uterine cavity the glandular structures are clearly marked. In some, it is true, the spaces are large and the epithelial lining is thrown into folds or exists in branching papillary processes, but in others the glands are small and are merely shown to be greatly multiplied and so numerous in parts that there is hardly any intervening tissue. In the deeper parts of the endometrium, close to the muscular tissue, one can generally find masses of epithelial cells which show little or no trace of glandular structure; the more advanced the disease, the more numerous are these collections of cells, and the deeper they are found in the uterine tissues.

In all of the cases of glandular cancer, a distinct growth was found in the uterine cavity; this was in most a diffuse growth from nearly the whole endometrium—generally there was an area which was unaffected (fig. 1); in other cases, the growth formed a more or less rounded tumour which sprung from a broad base (fig. 2).

I have not thought it advisable to record any cases of chorion-epithelioma in this paper, as this is a type of malignant disease which differs entirely in mode of origin, history, and prognosis from the usual types.

Symptoms. The only constant symptom of cancer of the body of the uterus is uterine hæmorrhage. It is noted in every one of my cases, and in all of them, with one exception, there is a note to the effect that it was profuse, or continuous, or frequent. In case 4 the notes are very insufficient; they merely

state that hæmorrhage was present for a year in small amount. In nearly all the cases this hæmorrhage occurred after a more or less definite menopause; in two cases there are no notes upon this point, and in other two it is definitely noted that the menopause had not come on. One of these (No. 2) was a case of sarcoma and fibroid, and the other (case 5) was in a patient of fifty-four who had irregular hæmorrhage for seven years. The occurrence, therefore, of hæmorrhage in the post-climacteric period is most suspicious. Intermenstrual discharge was noted in only four cases, and in only five cases of the eleven was there any offensive odour associated with the hæmorrhage or discharge. Pain was present in four cases, but in one of these it was only occasional, and in the other it is noted as only present when clots were passed. There was no definite wasting or loss of flesh in the large majority of cases; in only two was this noted as a symptom.

The average duration of the hæmorrhage, which we may take generally as the starting point of the symptoms, was from a year to eighteen months, but two of the patients had hæmorrhage for a much longer period. In case 5, hæmorrhage had been going on for seven years, and had been almost continuous for five years, while in case 10, the patient had suffered from irregular hæmorrhage for eleven years after sixteen years amenorrhœa. It is hardly possible that these patients can have been suffering from malignant growth during the whole of these long periods. In case 5, the menopause had not been passed, and probably there had been some chronic metritic change before the malignant growth began. In case 10, it is difficult to account for the long duration of the hæmorrhage coming after a well-established menopause, as the uterus showed nothing but glandular cancer.

It may be definitely stated from a study of the cases here reported that adeno-carcinoma of the uterus is a disease which advances slowly. In every case there was an interval of at least a year from the onset of suspicious symptoms to the date of operation, and then the disease in most of the cases was found localised in the mucous membrane and tissues immediately underneath; in only a few cases was the uterus penetrated to any great depth. It is possible that the pelvic glands may become involved at a fairly early period, but the results of operation do not indicate that this is a frequent occurrence.

Differential diagnosis. In cases of sarcoma of the body of the uterus the difficulty is generally to exclude fibroid tumour. We have to rely chiefly on the comparatively rapid development of symptoms associated with only moderate enlargement of the uterus. Occasionally there is an offensive discharge, and sometimes pain is a prominent feature, but neither of these symptoms is invariable, and both of them may be associated with fibroid tumour. If the uterus contains a fibroid as well as sarcoma, the diagnosis is very difficult and can never be quite definite. Our suspicions are aroused if there is a change in the character of the discharge, or if the general health of the patient shows rapid deterioration. In most cases of sarcoma of the body of the uterus, whether associated with fibroid or not, dilatation of the cervix followed by curetting is necessary to establish the diagnosis; sometimes the diagnosis is made only after removal of the uterus.

The differential diagnosis of cancer of the body generally presents no great difficulty; in the great majority of cases it is a post-climacteric disease. Hæmorrhage after the menopause should always excite our suspicions, and no elderly woman who suffers from uterine bleeding should be allowed to go unexamined. There are exceptional cases in which this bleeding may be caused by non-malignant affection. It may be due to (1) mechanical causes, (2) to mucous polypi, (3) to fibroid tumour, (4) to non-malignant endometritis.

Hæmorrhage may be caused by mechanical causes in elderly women when there is well marked prolapse, so that real ulceration is produced by friction of the mucous membrane. It may also result from the use of a pessary. In both of these cases, however, there is little difficulty in deciding as to the cause of the hæmorrhage. It is not uncommon to find a single mucous or fibroid polypus, or a crop of polypi in an elderly woman. These, of course, must always be regarded with some suspicion; but innocent polypi undoubtedly occur after the menopause and may give rise to bleeding. There are many cases recorded in which a fibroid tumour has occasioned profuse hæmorrhage after the menopause. I think we are justified in saying that a true fibroid of the uterus rarely, if ever, originates or increases in size after a well-defined menopause has been reached, but a tumour of this sort, which has previously given rise to little or no trouble, may begin to cause bleeding after many years of

amenorrhœa. This means that the tumour has become sub-mucous or polypoidal. In adult life an interstitial fibroid may be gradually driven towards the uterine cavity by the contractions of uterine muscle. In elderly women a corresponding change of position is probably due to atrophy of the tissue which lies between the tumour and the uterine cavity. In both cases the tumour travels in the direction of least resistance, and whenever its capsule projects into the uterine cavity, bleeding is almost certain to occur.

The fourth class of case in which hæmorrhage may occur from the uterine cavity apart from malignant disease is that of endometritis. While senile endometritis undoubtedly exists, it is rarely associated with hæmorrhage, and some writers deny the existence of such a condition. A case, however, which has come under my own observation proves that an inflammatory condition of the endometrium in a senile uterus may give rise to symptoms which are exactly those of cancer of the body. The patient was a married woman (multipara) of sixty years of age, who was admitted to St. Mary's Hospital in April, 1906, complaining of a yellow, offensive discharge, which had latterly been tinged with blood, and which had been going on for six weeks before admission. There was no pain, but she had lost flesh during the previous eight weeks. On examination, the discharge seemed so characteristic of cancer of the body of the uterus that I performed vaginal hysterectomy without a preliminary curetting. The appearance of the uterus is shown in fig. 9. It will be seen that the whole of the surface of the uterine cavity is studded with small, rounded projections. To the naked eye the appearance suggests a diffuse carcinoma. The microscope, however, failed to show any change typical of malignant growth. On the other hand, there was atrophy of glandular structures and increase of fibrous tissue elements in the endometrium (see figs. 10 and 11). Cases of this sort, occurring so many years after the menopause, must be extremely rare. Cases of chronic metritis with endometritis may very easily be confused with cancer of the body when they are found in women soon after the climacteric or before it is thoroughly established, but a diagnostic curetting should settle the question.

Results of operation. The operation performed in all my cases of malignant disease of the body of the uterus was vaginal hysterectomy, with the exception of one case (case 4) in which

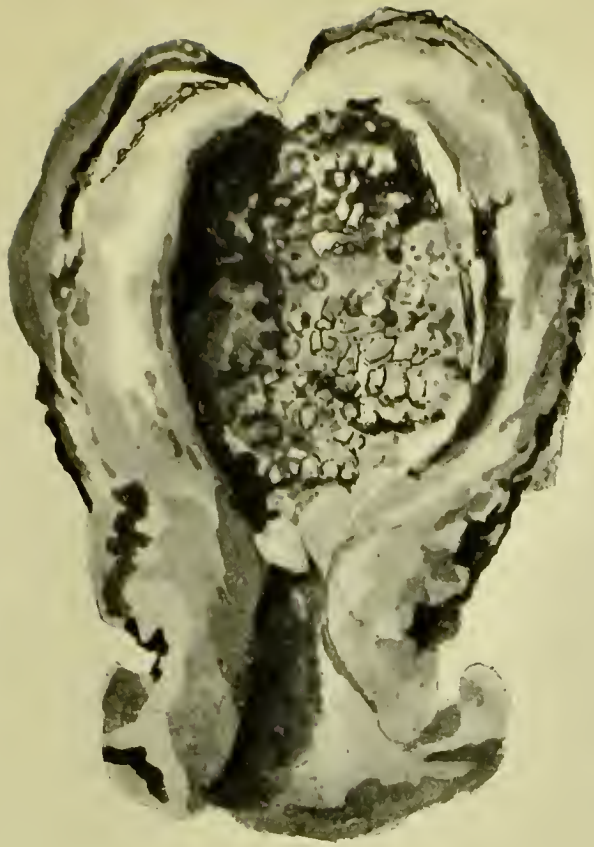


Fig. 9.—Non-malignant endometritis in a senile uterus.



Fig. 10.—Microscopic section taken from uterus shown in Fig. 9. The mucosa showing the gradual disappearance of the glands and the cellular condition of the interglandular stroma due to chronic inflammation. The photograph shows at its lower part the dilatation of a gland acinus with retention of contents and atrophy of the epithelium.

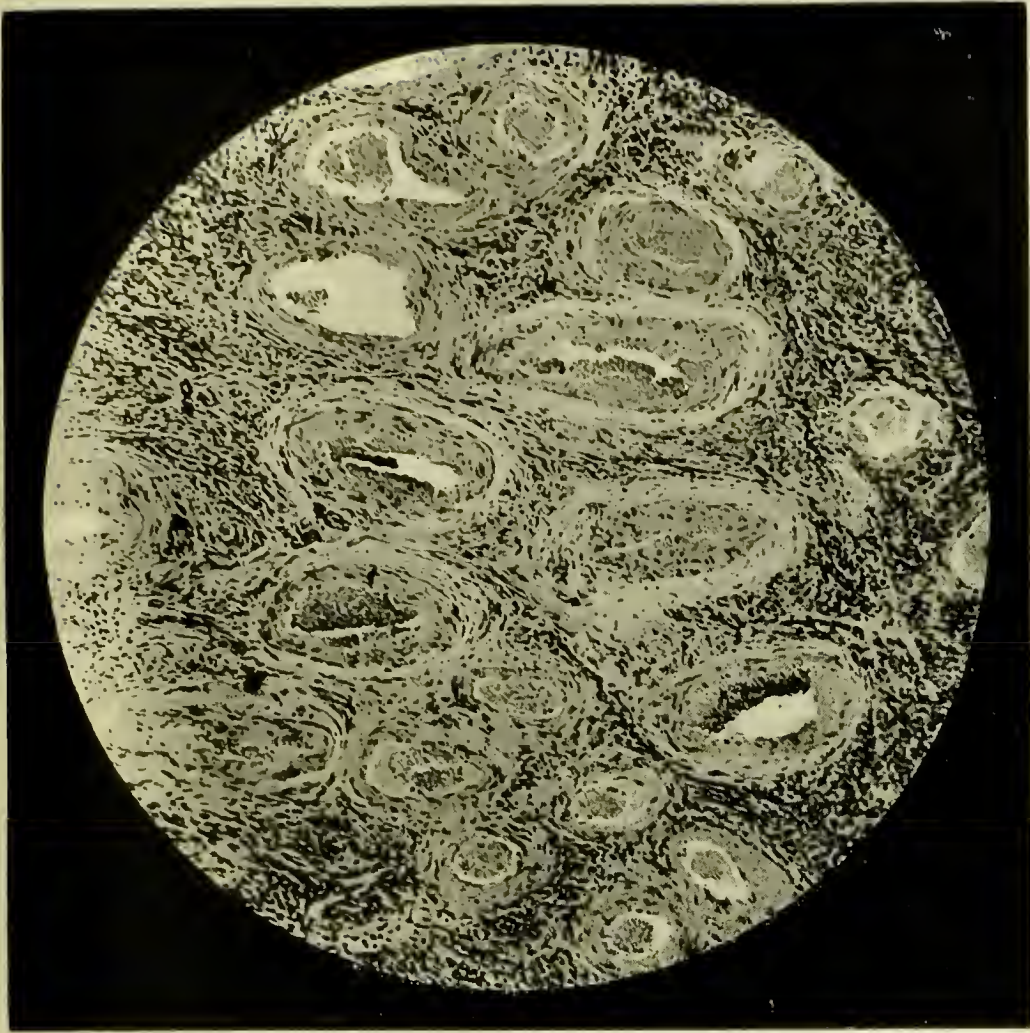


Fig. 11.—Section taken from uterus shown in Fig. 9. Group of blood- vessels situated in the inflamed mucosa and showing thickening of the walls by overgrowth of fibrous tissue which is undergoing hyaline degeneration. The surrounding tissue shows the cellular infiltration of chronic inflammation.

No.	Name, State, and Age	Number of Children and Date of last Confinement	Menopause	Symptoms	Nature and Date and Place of Operation	Disease	RESULT OF OPERATION.	
							Immediate	Remote
1	Mrs. G. W. 55	1 25 years ago	4 years before onset of symptoms.	Profuse hæmorrhage—1 year, not offensive, no intermenstrual discharge no pain.	Vaginal hysterectomy, 12th June, 1895 Nursing Home	Round celled sarcoma	Recovered	In good health at present date 12 years after operation.
2	Mrs. L. M. 50	3 16 years ago	Not passed	Profuse hæmorrhage—18 months, for 3 months constant discharge, sometimes sanguineous, sometimes watery, offensive, pain for some months latterly paroxysmal and acute.	Vaginal hysterectomy, 5th April, 1899 Nursing Home	Round and spindle-celled sarcoma invading fibroid growth.	Recovered	Recurrence—Death in October, 1900 about 18 months after operation.
3	Mrs. D. W. 67	3 30 years ago	20 years ago	Profuse hæmorrhage—6 months, no intermenstrual discharge, no pain.	Vaginal hysterectomy, 28th Feb., 1902 Nursing Home	Glandular carcinoma	Recovered	In good health 2 years after operation, since then not heard of.
4	Mrs. G. M. 52	0	Not noted	Hæmorrhage for a year—small in amount.	Abdominal hysterectomy, 23rd March, 1904, St. Mary's Hospital	Glandular carcinoma	Recovered	Died Sept. 18th, 1904, 6 months after operation, presumably from recurrence.
5	Mrs. J. M. 54	1 13 years ago	Not passed	Irregular hæmorrhage for 7 years—almost constant for 5 years, offensive watery discharge, pain only on passing clots.	Vaginal hysterectomy, 9th April, 1904 St. Mary's Hospital	Glandular carcinoma	Death 48 hours after operation.	—
7	Mrs. M. M. 51	1 20 years ago	Not noted	Hæmorrhage for 9 months offensive for 4 months, constant pain in hypogastrum 9 months, loss of flesh.	Vaginal hysterectomy, 17th Jan., 1905 St. Mary's Hospital	Glandular carcinoma	Recovered	Died Aug. 19th, 1906, 19 months after operation, presumably from recurrence.
7	Miss R. 49	—	Not definite, long intervals between periods, a year before onset of symptoms	Hæmorrhage for nearly 12 months, lately continuous, no other symptom.	Vaginal hysterectomy 11th April, 1905 Nursing Home.	Glandular carcinoma	Recovered	In good health at present date.
8	Mrs. P. M. 51	9 13 years ago	4 years before onset of symptoms	Continuous hæmorrhage from Feb. to Sept., offensive intermenstrual discharge, pain occasionally in hypogastrum for 2 months, loss of flesh for 2 months.	Vaginal hysterectomy 27th Sept., 1905 St. Mary's Hospital.	Glandular carcinoma	Recovered	In fair health at present date.
9	Mrs. M. W. 65	6 21 years ago	13 years before onset of symptoms	Irregular hæmorrhage for 12 months, latterly frequent and in fair quantity no other symptoms.	Vaginal hysterectomy, 11th Nov., 1906 Nursing Home.	Glandular carcinoma	Recovered	In good health at present date.
10	Mrs. H. W. 66	1 38 years ago	No periods from the age of 39 to 55	11 years irregular hæmorrhage, latterly some intermenstrual discharge watery but not offensive, no pain.	Vaginal hysterectomy, 18th May, 1907 St. Mary's Hospital.	Glandular carcinoma with change to squamous epithelioma.	Recovered	In good health at present date.
11	Mrs. R. W. 67	2 22 years ago	16 years ago	Hæmorrhage for 12 months about once a week, not very profuse, rather offensive, no pain.	Vaginal hysterectomy, 9th Oct., 1907. St. Mary's Hospital.	Glandular carcinoma	Recovered	—



abdominal hysterectomy was performed on account of the large ness of the uterus and the narrowness of the vagina. In the nine operations for adeno-carcinoma, one was fatal (case 5). Death occurred in two of the remaining eight cases as a result of recurrence of the growth (cases 4 and 6); in one, six months, and in the other nineteen months after the operation. Up to the present time there has been no recurrence in the remaining six cases, but in two of these only a short period (seven months and three months) has elapsed since the operation. Three of the remaining four patients are well after intervals varying from thirteen to twenty months. The fourth patient cannot be traced, but she was known to be well two years after the operation. These results, so far as recurrence is concerned, are not so good as statistics would have led me to expect. At the best, there is only absence of recurrence in six cases out of eight. I think the explanation of this is to be found in the fact that the disease in both of the cases in which it recurred was very advanced at the time of operation. In one (case 4) the uterus was very much enlarged, and in the other (case 6) the microscopic sections showed that the cancer had penetrated deeply into the muscle.

Of the two patients who suffered from sarcoma, one is alive and well after an interval of $12\frac{1}{2}$ years, but the other died from recurrence 18 months after operation.

In conclusion, I have to thank Professor Lorrain Smith for much valuable help and advice. He has gone over each specimen with me, and has carefully examined each microscopic section and has written the description underneath each microphotograph. Dr. W. Fletcher Shaw, House Surgeon to St. Mary's Hospital, has given me much assistance, as he has collected for me many of the notes, specimens, and microscopic sections which form the groundwork of this communication.

CHOLESTERIN: SOME ACCOUNT OF ITS CHEMICAL, PHYSICAL, AND BIOLOGICAL RELATIONS.

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IN the latter part of the 18th century Conradi (1775) and Gren (1788) remarked upon the existence in gall-stones of a peculiar substance, which, from its general characters and its behaviour towards solvents, they regarded as being of a fatty nature and accordingly termed it gall-stone fat. Fourcroy, subsequently, coming to a similar conclusion, classed it along with Spermaceti and Adipocere, which expression of its chemical relationship was maintained until Chevreul (1815) demonstrated certain differential features and gave it the name of Cholesterin.

Subsequent investigations have established this constituent of the gall-stone as a well-defined chemical entity more closely allied to the Terpenes than to the Fats and as one, and the most definitely characterised, of a group of closely allied or isomeric substances widely distributed in organic nature. By repeated and careful analyses and by histological investigations it has been shown not only that cholesterin is a not infrequent phenomenon of many retrograde pathological processes, but that it, or some substance isomeric with it, is a constant constituent of every normal tissue, animal and vegetable; a distribution which by its constancy and range would seem to proclaim for cholesterin and its congeners a fundamental and constitutive significance. To the human physiologist and pathologist, however, cholesterin appears to have chiefly claimed attention in its more manifest and pathological sequence and particularly so as a factor in that much belaboured problem—the gall-stone—while the more essential and fundamental biological problems which these substances must sustain have in consequence been over-shadowed and to some extent lost sight of. It thus appeared that some useful purpose might be served by an

estimate of our present knowledge of cholesterin and its congeners in their chemical, physical, and biological relations, and this has been undertaken the more readily, as the writer, attracted some years ago to this recondite province of biochemistry, has intermittently pursued investigations into these aspects of the subject and with results, which though barely commensurate with the energy expended, have by accumulation apparently attained an importance that merits their record.

THE PHYSICAL AND CHEMICAL PROPERTIES OF CHOLESTERIN.

Cholesterin (Cholesterol : Cholestenol) as obtained from the gall-stone or from nervous tissue is an odourless, somewhat unctuous, colourless, crystalline substance, insoluble in water, in solutions of the caustic alkalies, and in dilute mineral acids; on the other hand, it is soluble in most organic solvents and more abundantly on heating, it is readily soluble in chloroform, ether, acetone, ethyl acetate, carbon bisulphide, benzene, etc., at ordinary temperatures, less so in petroleum ether, volatile and fatty oils, in fatty acids, in the salts of the bile acids, and still less in solutions of soaps. In ethyl alcohol it is only slightly soluble in the cold but readily so in boiling alcohol.

Absolute ethyl alcohol, 17°·5C. dissolves 1·086 % (Hürthle).

Ethyl alcohol, Sp. Gr. 0·84 boiling dissolves 11·09 % (Chevreul).

„ „ 0·82 „ „ 20 % (Chevreul).

Petroleum ether, Sp. Gr. 0·7522, at 19°C. dissolves 0·832 % (Bömer).

„ „ 0·7522, at 23°C. „ 1·038 % (Bömer).

In solution cholesterin is optically active, exerting a lævoptatory effect on a beam of plane polarised light. Its specific rotatory power has been determined for ethereal solution to be :—

$$\alpha_D^{15^\circ} = -31\cdot59 \text{ (8 grammes in 100cc. ether).—Lindenmayer.}$$

$$\alpha_D^{15^\circ} = -31\cdot12 \text{ (2 grammes in 100cc. ether).—Hesse.}$$

$$\alpha_D^{15^\circ} = -29\cdot92 \text{ (4·6 grammes in 100cc. ether).—Burian.}$$

My own determinations accord very closely with those of Burian.

The average of three observations on cholesterin from gall-stones gave :—

$$\alpha_D^{15^\circ} = -30\cdot31 \text{ (2·998, 3·897, 4·576 grms. in 100cc. ether).}$$

The average of two observations on cholesterin from blood gave :—

$$\alpha_D^{15^\circ} = -29.65 \text{ (3.001, 3.879 grms. in 100cc. ether).}$$

The average of three observations on cholesterin from brain gave :—

$$\alpha_D^{15^\circ} = -30.01 \text{ (3.8772, 5.312, 6.0012 grms. in 100cc. ether).}$$

For chloroform solution the specific rotatory power is :—

$$\alpha_D^{15^\circ} = -36.61, 0.249d. \text{ (2.8 grms. in 100cc. chloroform).—Hesse.}$$

From its solution in dry ether, chloroform, petroleum ether or benzene, cholesterin crystallises out in slender, silky needle-shaped crystals free from solvent; from boiling alcohol it crystallises out on cooling in transparent, glistening rhombic plates having acute angles of $76^\circ 30'$ or $87^\circ 30'$, the plates increase in size as the rate of cooling is diminished, they are commonly of exceeding thinness and frequently overlies in such a manner as to give rise to the well known and often ambiguously described appearance of a rhombic plate with "a corner cut out." During the separation from hot alcoholic solution the initial crystals often appear to be of the acicular type, as a result of blunting of the obtuse angles and narrowing of the acute angles, but gradually pass into the true rhombic form.

From dilute alcohol it has long been held that cholesterin crystallises in combination with one molecule of water (Heinz), the rhombic plates on exposure to a dry atmosphere readily split and become opaque, gradually losing their water of crystallisation. From anhydrous ethyl alcohol I have determined that cholesterin separates in combination with a molecule of alcohol in the typical rhombic plate, and in this resembles cholalic acid (Mylius).

Similarly from other solvents, ethyl acetate and the fatty acids cholesterin crystallises out associated with apparently an equimolecular proportion of the solvent.

Pure cholesterin melts sharply, without decomposition, at 145° — 146°C. (148.5°C. corr: Reinitzer). It can be distilled unchanged in vacuo above 360°C. , and also under ordinary

pressures with careful heating. Its molecular refraction as determined by Kanonnikow is 200·88, and its molecular heat of combustion (constant volume) is 3836·4 cal. (Berthelot and Andre).

The empirical formula of cholesterin is not yet definitely established, the majority of determinations agree in that the molecule contains 27 carbon atoms and one oxygen atom, but differ with regard to the number of hydrogen atoms. According to Mauthna and Suida and van Oordt $C_{27}H_{44}O$ is the more probable formula, whilst other analyses as those of Reinitzer and Obermüller giving $C_{27}H_{46}O$ have been accepted by Diels and Abderhalden and recently by Windaus. A difference of two hydrogen atoms in a substance of such high molecular weight as cholesterin is one of extreme difficulty to establish and this technical difficulty is further increased by the facility with which cholesterin and its derivatives undergo inequable and incomplete combustion. From determinations of the molecular weight by Raoult's method, Abel concludes in favour of the composition $C_{27}H_{44}O$, which formula will be accepted in the present article.

By many reactions to which cholesterin is disposed it appears that the solitary oxygen atom of the molecule is contained in a secondary alcoholic hydroxyl group (CHOH), thus with acid anhydrides $(RCO)_2O$ and acid chlorides $(ROCl)$ it reacts with the formation of ethereal salts or esters $C_{27}H_{43}OOCR$; with phosphorous pentachloride PCl_5 or thionyl chloride $SOCl_2$ it reacts in such a way that the hydroxyl (OH) group is replaced by chlorine giving cholesteryl chloride $C_{27}H_{43}Cl$, which on reduction is converted into the hydrocarbon cholesten $C_{27}H_{44}$; acted on in petroleum solution with metallic sodium or potassium, crystalline sodium or potassium cholesterylate is formed, and further, by the action of such dehydrating agents as phosphorous pentoxide, anhydrous copper sulphate, etc., water is abstracted from the cholesterin molecule leaving a mixture of isomeric hydrocarbons—cholesterylenes $C_{27}H_{42}$ —of varying optical activity and melting at from 79° — $80^{\circ}C$. On oxidation with CuO the hydroxyl containing group is changed into a ketonic group.

Further, since cholesterin readily takes up one molecule of a halogen— Br_2 , Cl_2 , I_2 —forming stable crystalline addition products, e.g., cholesterin dibromide (dibrom-cholestanol) $\text{C}_{27}\text{H}_{43}\text{Br}_2\text{OH}$, or one molecule of hydrogen chloride forming cholesterin hydrochloride (chlor-cholestanol) $\text{C}_{27}\text{H}_{44}\text{ClOH}$, it appears that the cholesterin molecule is unsaturated to the extent of two hydrogen atoms and that accordingly it possesses a double linking between two of its carbon atoms.

It may thus be regarded as established that cholesterin is an unsaturated secondary alcohol $\text{C}_{26}\text{H}_{42}\text{CHOH}$, derived from the unsaturated hydrocarbon cholesten $\text{C}_{27}\text{H}_{44}$, and, being optically active, that its molecule contains at least one asymmetrically disposed carbon atom. Beyond this very little is as yet demonstrated of its molecular constitution.

The not inconsiderable labours which such investigators as Mauthna and Suida, during the last twenty years, and Windaus, and Diels and Abderhalden, during more recent years, have expended on attempts to elucidate the problem of the constitution of cholesterin have so far yielded insignificant results, making us acquainted with certain peculiarities of the fringe of the large molecule and serving by analogy to more and more confirm the early speculations of Walitzky, Liebermann, and Weyl that the substance belongs to the complex terpenes.

Consideration of the formula of the unsaturated hydrocarbon cholesten $\text{C}_{27}\text{H}_{44}$, from which cholesterin is derived or of the corresponding hypothetical saturated hydrocarbon cholestan $\text{C}_{27}\text{H}_{46}$, shows by the deficiency in the number of hydrogen atoms in the molecule to accord with either the normal paraffins— $\text{C}_n\text{H}_{2n+2}$ —or the olefines— C_nH_{2n} —that these bodies must be wholly or in part of cyclic structure, and from the manner in which cholesterin reacts with cold concentrated nitric acid it would further appear that the rings constituting the cholesterin molecule are reduced rings and that the molecule contains no structure corresponding to the benzene ring. When cold concentrated nitric acid reacts with a benzene derivative, characteristic aromatic nitro- compounds are formed, but under similar conditions as shown by Mauthna and Suida and Windaus cholesterin yields a nitrosate or nitrosite by a reaction analogous to that

investigated by Tönnies and Wallach in the nitration of phellandrene.

Cholesten, which then may be regarded as being built up, wholly or in part, of reduced rings, is obtained by the reduction of cholesteryl chloride; it crystallises in colourless needles, melting point 89° — 90°C. , and is lævorotatory, $\alpha_D = -56.29$ (chloroform solution) Mauthna and Suida. Like its alcohol cholesterin, it readily takes up one molecule of a halogen, forming addition products, which on reduction yield, not the saturated dihydrocholesten or cholestan, but the original hydrocarbon cholesten. This peculiar behaviour of the halogen addition products of cholesten on reduction is equally characteristic of those of cholesterin itself, and from this Mauthna and Suida conclude that the double bond in the original molecule is not of the usual ethylene type— $\text{HC}:\text{CH}$ —but probably $\text{H}_2\text{C}:\text{C}<$. Towards reducing agents cholesterin equally with its dihalogen derivatives is peculiarly resistant, and until quite recently all attempts at the production of the hydrocarbon cholestan had proved abortive, and it remained known only in a series of derivatives in which the saturation was completed in other ways than by the interpolation of a molecule of hydrogen. An exception to this statement apparently exists in the substance discovered by Bondzýński and Humnicki, coprosterin, which they regard as dihydrocholesterin $\text{C}_{27}\text{H}_{45}\text{OH}$, but this I shall have occasion to discuss later. In 1906, however, Diels and Abderhalden, and Neuberg announced independently that by the action of metallic sodium in boiling amyl alcohol on cholesterin a product is obtained which is dextro-rotatory, melting point 119° — 126°C. , and which is incapable of adding a molecule of a halogen. This product they regard as resulting from saturation of the cholesterin molecule by two atoms of hydrogen— $\text{C}_{27}\text{H}_{45}\text{OH}$ —dihydrocholesterin or α cholestanol, that is, the alcohol having the same relation to the saturated hydrocarbon cholestan as cholesterin bears to the unsaturated hydrocarbon cholesten.

Whilst Diels and Abderhalden maintain that this α cholestanol has no relation to the substance coprosterin, Neuberg, on the other hand, regards the latter as an impure α cholestanol; an

interesting reflection on the curiously accurate combustions of Bondzyński and Humnicki. Still more recently, Windaus succeeded in obtaining a product identical with this α cholestanol by the action of preformed sodium amylate on cholesterin, and he regards it not as reduction product, but as a cyclo-cholesterin produced by a transformation of the olefine linking of the cholesterin molecule into a cyclic linking, a change which, whilst rendering the substance saturated, does not entail the addition of a molecule of hydrogen. It thus appears doubtful whether reduction products of cholesterin have even yet been obtained.

Towards oxidising agents cholesterin is much less resistant. Even when maintained at a temperature of from 95° — 100°C . for a few days in the drying oven it gradually becomes discoloured, and its melting point is lowered, a change, as shown by Mauthna and Suida, to be due to slight oxidation. In a specimen which had been exposed at a temperature of 96°C . for four weeks these observers found an increase of 2 per cent. of oxygen. More recently it has been pointed out by Schultze and Winterstein that cholesterin exposed to sunlight in the presence of air also undergoes slow oxidation, its melting point in two years being lowered to 115° — 137°C . and 108°C ., an effect which was also noted to occur in the case of other members of the cholesterin group.

Cholesterin shaken up with an ethereal solution of hydrogen peroxide, "ozonic ether" so-called, also, as I noted some time ago, has its melting point considerably lowered, a result, I believe, of oxidation.*

The more vigorous oxidation of cholesterin by such agents as nitric acid, chromic acid, hypobromic acid and potassium permanganate, which has been undertaken by all investigators with a view to the elucidation of its molecular structure, has yielded, among the better characterised products, a series of derivatives of cholesten and cholestan, and in many instances the reaction would appear to run in an analogous way to well-defined oxidations in members of the terpene series of known constitution.

*The products obtained by this method of oxidation have not been investigated, although it is possible that such may yield information of constitutive importance.

The earlier investigators obtained amorphous substances of doubtful constitution and of little significance. To Mauthna and Suida belongs the credit of having been the first to obtain definite crystalline products of oxidation.

Employing chromic acid, they obtained as chief products of oxidation three neutral substances :—

α Oxycholestenol— $C_{27}H_{42}O_2$ —an unsaturated secondary alcohol, in which the function of the second oxygen atom, which is also present in the other products, could not be determined.

Oxycholestenon— $C_{27}H_{40}O_2$ —the corresponding ketone, in which it was left undecided whether it still contained the double bond.

Oxycholestendiol— $C_{27}H_{42}O_3$ —the glycol, which was readily transformed by dehydration into oxycholestenon.

From cholesteryl chloride the chief product obtained was oxychlorcholestenon— $C_{27}H_{43}OCl$ —and from cholesteryl acetate they obtained the acetyl derivatives of the above substances.

These results were confirmed by van Oordt, and he found that on attempting to obtain oxycholestenon from the oxycholestendiol by means of alcoholic hydrogen chloride the chief product was a substance which, Windaus showed, was the ethyl ester of oxycholestenon. In this he was able to prove the existence of a carbonyl group—CO—and accordingly concluded that the second oxygen atom of oxycholestenon, whose function had been in doubt, must exist in a hydroxyl group, probably in tertiary combination. Windaus concluded that in the oxidation of cholesterin the first stage is the change of a tertiary CH group to C·OH (oxycholestenol), and, further, the oxidation of the secondary CH·OH group to CO (oxycholestenon). In both these products a double bond should still exist. On reducing oxycholestenon he obtained a saturated diketone—cholestandion $C_{27}H_{42}O_2$ —which he had previously obtained by the oxidation of cholestanon-ol; from this he concluded that oxycholestenon must be an unsaturated diketone in which one of the CO groups may react in the enolic form. Oxidising cholestandion, he obtained a ketodicarboxylic acid— $C_{27}H_{42}O_5$. This change, corresponding with the formation of camphoric acid from camphor, would indicate the existence in cholestandion of a ring

containing a group—CO—CH₂—which on oxidation splits at the ketonic group. The ketodicarboxylic acid yielded a stable anhydride from which it would appear that the carboxyl groups must occupy the 1 : 5 positions. Continuing on these lines, Stein, starting with chlorcholestenon C₂₇H₄₃OCl, obtained an oxydicarboxylic acid, and on further oxidation a ketodicarboxylic acid, and, finally, with the opening of a ring, a tetracarboxylic acid. Windaus having previously shown by his results the probability of the secondary OH group of cholesterin being situated in a reduced ring, this work of Stein would seem to indicate the existence of a second reduced ring in the molecule in which is contained the double bond.

Employing potassium permanganate as the oxidising agent, Windaus obtained a product containing three OH groups, Triol, which on further oxidation with CrO₃ gave a body isomeric with the oxycholestendiol of Mauthna and Suida; this trioxy substance would thus appear to be the alcohol corresponding to the saturated diketo-alcohol, oxycholestendiol.

Diels and Abderhalden, using sodium hypobromite, obtained from cholesterin a dicarboxylic acid—C₂₇H₄₄O₄—which, like camphoric acid, yields an acid ester on direct esterification, the neutral ester being obtained by reacting on the silver salt with alkyl iodide. From this they conclude that whilst one of the carboxyl groups is in the primary or secondary position the other is tertiary, and since cholesteryl chloride under similar conditions does not yield this acid, it follows that the oxidation begins at the OH group of the cholesterin molecule.

In 1903 Pickard and Yates announced that they had obtained from cholesterin by oxidation, arachidic acid—C₂₀H₄₀O₂—which would indicate that the cholesterin molecule contains a normal chain of 19 carbon atoms; this statement has, however, not been confirmed.

More vigorous oxidation with hot concentrated nitric acid yielded to Mauthna and Suida certain amorphous tetrabasic acids readily soluble in water and which appeared to be carboxylic derivatives of hydrocarbons having the formula C_nH_{2n}.

Windaus by similar means obtained, among the products of

oxidation, dinitroisopropane, from which he concluded that the cholesterin molecule contains the group $(\text{CH}_3)_2\text{C}<$.

The results of the investigations into the constitution of the cholesterin molecule thus far obtained would seem to afford reasonable ground for regarding this substance as constituted by a series of reduced rings, and that it accordingly belongs to a class of substances quite distinct from the three great constitutive classes of animal substances—proteids, fats and carbohydrates—namely, the terpenes, representatives of which have hitherto invariably been associated with plant life.

Reactions of Cholesterin: The properties which appear most useful for the identification of cholesterin are the melting point and the specific rotatory power. Beyond these cholesterin and its derivatives give certain colour reactions which usefully serve the same purpose.

1. Hesse-Salkowski reaction. On the addition of an equal volume of concentrated sulphuric acid to a solution of cholesterin in chloroform and slightly shaking, the chloroform solution becomes blood red and changes to cherry red and then to purple; with only a trace of cholesterin the colour is lemon yellow, on being poured off into a basin the chloroform solution becomes blue, then green, and finally yellow. The layer of sulphuric acid below the chloroform presents a green fluorescence and on the addition of acetic acid it becomes rose or purple red with a green fluorescence.

2. Liebermann-Burchard reaction. Cholestal reaction. On the addition of acetic anhydride—and concentrated sulphuric acid—drop by drop to a solution of cholesterin in dry chloroform, the fluid becomes rose red, then violet, blue, and finally green. Even with traces only of cholesterin this reaction appears within a few minutes.

3. Obermüller's reaction. Dry cholesterin melted with a few drops of propionic anhydride gives on cooling a brilliant play of colours: violet, blue, green, orange, and copper red in this order, which are particularly well seen when some of the molten substance is allowed to cool on a glass rod held against a black back-ground.

4. Schiff's reaction. A mixture of cholesterin, chloroform,

hydrochloric acid, and a trace of ferric chloride is evaporated in a basin till the edges begin to assume a violet-red colour, then after cooling more chloroform is added, the mixture evaporated to dryness and heated, when it becomes purple, then blue, and finally green.

5. Neuberg and Rauchwerger's reaction. A solution of δ Methylfurfural is added to an alcoholic solution of cholesterin, then on the addition of the same volume of concentrated sulphuric acid a red ring appears at the junction of the two fluids, and on shaking, the fluids being kept cool, the whole fluid assumes this colour and spectroscopically gives an absorption band from E to b.

This reaction is also given by phytosterin, bile acids, and a large series of hydroxyl containing compounds.

6. Hirschsohn's reaction. A solution of trichlor-acetic acid in hydrochloric acid gives a red colour with cholesterin.

7. As a microscopic reaction. Crystals of cholesterin on treatment with concentrated sulphuric acid and a trace of iodine are coloured violet, then blue, green, and finally red.

Certain differences have been established in the reactions of the derivatives of cholesten and cholestan. The Hesse-Salkowski reaction is specially characteristic of members of the cholesten series, those of the cholestan series yielding either an insignificant or no colour reaction with sulphuric acid. The Liebermann-Burchard reaction on the other hand is given by members of both series.

RELATION OF CHOLESTERIN TO FATTY ACIDS, FATS AND SOAPS : In describing the solubility relations of cholesterin it was incidentally mentioned that this substance is soluble in fatty acids, in neutral fats (glyceryl esters), and slightly in the sodium and potassium salts of these acids (soaps). This property may, in view of the existence of cholesterin in the tissues in a dissolved form be possessed of some importance, and accordingly calls for further consideration.

*Cholesterin and Fatty Acids.** It has long been recognised

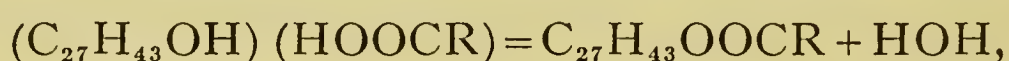
* Details of this particular branch of my investigations in which a comparison of the physical properties—melting point, rotatory power, depression of freezing point of solvents—of the cholesterin acid mixtures and the cholesteryl esters is being worked out, will be published subsequently.

that cholesterin is soluble in certain fatty acids on heating, and particularly so in acetic acid, and that from solution in the latter it crystallises out in combination with one molecule of the acid (of crystallisation) in needle-shaped crystals which melt sharply at 110°C. , and on heating to 120°C. are decomposed into their two components, as also happens when the crystals are treated with water or alcohol (Lindenmayer). Similarly two molecules of cholesterin will crystallise out in combination with one molecule of oxalic acid, which association seems to be of a similar nature to the foregoing.

This peculiarity of cholesterin to crystallise out from its solution in a fatty acid in combination with an equimolecular proportion of the fatty acid has apparently been misunderstood inasmuch as some recent observers have regarded this association as being of the nature of an ethereal salt. Salkowski in a recent paper gives as a method for the preparation of the cholesterin esters of palmitic acid and stearic acid, etc., that the acid and the cholesterin dissolved in ether be mixed in equimolecular proportions, when on the addition of 95 per cent. alcohol the ester required will be thrown down in a pure form and of the correct melting point. My own observations on the relation of cholesterin to the fatty acids appear to indicate that whenever cholesterin crystallises out from solution in a fatty acid, or from a mixture in equimolecular proportions of cholesterin and a fatty acid dissolved in some anhydrous solvent (petroleum-ether, benzol, ether), it invariably does so in combination with one molecule of the acid in uniform needle-shaped crystals of definite melting point, generally lower than that of the true ester. So far as these observations have proceeded this relation has been established for formic, acetic, propionic, butyric, oleic, palmitic and stearic acids, and accordingly it would seem to be a general phenomenon.

The true nature of the association is at once evident from the action on the crystals of water, alcohol, solutions of the alkaline carbonates and by heating them to a temperature above their melting point, any of which suffices to withdraw the acid from combination leaving the cholesterin which gives its true melting point.

It would thus appear that we have to do with a purely physical association which is non-existent in solution and only comes into being with the phenomenon of crystallisation, that the relation of the acid to the cholesterin is that which obtains between water or alcohol and cholesterin when the latter crystallises from moist or anhydrous alcohol. These physical associations of cholesterin and fatty acids can, however, be readily converted into the true esters by the abstraction of water—



as happens when they are heated in the presence of a considerable excess of acid. The compounds so obtained are unaltered by water, alcohol or sodium carbonate, and are only with considerable difficulty saponified by the caustic alkalies.

Ethereal Salts of Cholesterin. These are most readily obtained by the action of acid anhydrides— $(\text{RCO})_2\text{O}$ —or acid chlorides— RCOCl —on dry cholesterin, and in a yield approximating to the theoretical; they are also produced as has already been indicated by heating cholesterin with four to six times the theoretical amount of the dry acid, the yield is comparatively poor and the purification of the product is tedious: the general method of acting on cholesteryl chloride with the silver salt of the acid is in my experience a reaction that is extremely difficult to conduct and proceeds very incompletely: a further method of which I have had experience, that of introducing dry hydrogen chloride into a mixture of cholesterin and the fatty acid, either with or without zinc chloride, also gives a poor yield and a product that requires much purifying.

By one or other of the first three methods a large number of these ethereal salts have been prepared of the fatty and also of the aromatic acids, and their properties investigated by Berthelot, Obermüller, Hürthle, Lehmann, and Jaeger.

In a pure state the cholesteryl esters are well defined crystalline substances, less easily saponifiable than the ordinary fats, and having a solubility less than cholesterin itself especially so in alcohol, a property which is of use in their purification.

Many of them, especially those of the lower fatty acids, exhibit a beautiful play of colours when passing from the molten

to the solid state, a property which is the basis of Obermüller's characteristic reaction for cholesterin.

As was first pointed out by Lehmann, certain of the cholesteryl esters exhibit during the passage from the solid to the molten isotropic fluid state, an intermediate anisotropic phase in which the substance, whilst possessing all the physical characteristics of a fluid has a turbid appearance and is doubly refractive: the existence of this anisotropic or fluid crystalline phase has been proved by Jaeger for a large series of cholesteryl esters prepared by himself, and he has shown that whilst in certain esters the phase is one of considerable stability in others where previously its existence was not suspected it is extremely labile under ordinary pressure relations and can only be demonstrated on the rapid cooling of the isotropic molten substance to a temperature below its melting point.

It would further appear from the investigations of Lehmann and Jaeger that the anisotropic phase consists of at least two distinct phases or in some cases, e.g., cholesteryl cinnamylate of a series of phases. This phenomenon which is also exhibited by certain azoxy-compounds is of doubtful significance, it has been regarded as being caused by the presence of impurities or at least of isomeric substances. Jaeger, however, who failed to observe it in the esters of phytosterin which as will be pointed out is probably a mixture of at least two substances, believes it to be essentially a constitutive property. Adami and Aschoff investigating this phenomenon in its biochemical relations apparently endowed it with a significance far more exclusive than their methods could possibly permit, and Powell White from a more extensive examination of the various factors involved, has demonstrated that the existence of an anisotropic fluid even when it contains cholesterin does not necessarily imply the presence of cholesteryl esters.

The esters which it is believed exist preformed in the tissues of the animal organism are those of oleic, palmitic, and stearic acids. These esters as isolated from blood serum and prepared synthetically were found by Hürthle to have the following properties:—

Cholesteryl oleate: Crystallises in long thin colourless

needles; melting point $42^{\circ}\text{C}.$, $\alpha_D = -18.48$ ($d = 7.94$, alcohol + chloroform). Its solubility in absolute alcohol at $17^{\circ}.5\text{C}.$ is .398%. It gives the cholesterin reactions in a modified form.

Cholesteryl palmitate: Crystallises in silky platelets which rapidly become opaque and white; melting point 77° — $78^{\circ}\text{C}.$ It is less soluble than the oleate, and gives the cholesterin reactions in a still more imperfect manner.

Cholesteryl stearate: Crystallises in white platelets, melting point $82^{\circ}\text{C}.$ ($85^{\circ}.5\text{C}.$ Herbig), it is less soluble than the palmitate.

It is generally stated that the esters of cholesterin possess the property of absorbing considerable quantities of water, swelling up into a fatty mass, ordinary lanoline being regarded as a mixture of such hydrated cholesteryl and other esters. A number of pure synthetic esters which I have prepared including the oleate and the palmitate, give no indication of this property, whilst I have repeatedly noted that it is a striking phenomenon of the physical mixtures of cholesterin and fatty acids, and to a less extent also of cholesterin and neutral fats.

Cholesterin and Neutral Fats: Cholesterin dissolves on heating in all neutral fats. This mixture as I have noted forms a more permanent emulsion with water than does the fat alone, and if a large amount of cholesterin is employed, namely equal weights, a thick greasy mass is obtained, which swells up with water in a manner which is usually ascribed to the esters of cholesterin.

From this mixture of cholesterin and fat, it is practically impossible to isolate the cholesterin without resorting to saponification, and by fractional crystallisation from hot alcohol one occasionally obtains needle-shaped crystals, which, however, give no constant melting point.

Cholesterin and Soaps: Cholesterin is soluble to a slight extent in sodium and potassium salts of the fatty acids and more abundantly in those of taurocholic and glycocholic acids (Bile salts).

COPROSTERIN: This substance isolated by Bondzyński (1896) from human fæces, and apparently the principal constituent of the Excretin of Marcet (1860) and Hinterberger (1873) and of the

Stercorin of Flint (1862), would appear from the investigations of Bondzynski and Humnicki to be a reduction product of cholesterin. From the latter it differs in several particulars, it is more readily soluble than cholesterin and from cold absolute alcohol in which it is easily soluble it crystallises in long thin needles; its melting point is 95° — 96°C. , it is dextrorotatory, its specific rotation being $\alpha_D = +24^{\circ}$. It gives the colour reactions of cholesterin in a modified form, it does not, however, give Obermüller's reaction.

As this substance refuses to add a halogen molecule it would appear that its molecule is saturated. Like cholesterin, it contains a hydroxyl group and yields a number of well characterised esters.

The analyses of coposterin and certain of its esters by these two observers indicate that its empirical formula is $\text{C}_{27}\text{H}_{48}\text{O}$ and accepting cholesterin as $\text{C}_{27}\text{H}_{46}\text{O}$, they regard it as dihydrocholesterin.

In view of the conclusions of Bondzynski and Humnicki, it is of interest to note that all attempts to reproduce this substance *in vitro* by the reduction of cholesterin—both by chemical and bacterial methods of reduction—have so far yielded negative results. The recent investigations of Neuberg and of Diels and Abderhalden which have already been referred to, in which they believe they obtained the dihydrocholesterin are particularly noteworthy, as, assuming that the product which they obtained had this nature, it presents very striking differences from the apparently very homogeneous substance isolated by Bondzynski. Further, it is of interest to note that where the saturation of the cholesterin molecule is brought about by halogens, the optical activity of these halogen derivatives of cholestanol is like that of cholesterin itself lævorotatory.

Working at the time (1904) with W. J. Pope, all methods of reduction were employed, including metallic sodium in boiling amyl alcohol, but we were unable to obtain from cholesterin any product having the properties of Bondzynski's coprosterin.

More recently (1906) repeating the observation of Bondzynski

and Humnicki that cholesterin administered to the human subject is excreted as coprosterin, I obtained a negative result. Five grammes of pure cholesterin mixed with butter was administered to a healthy subject, and from the fæces 4·6 grammes of cholesterin were isolated, but no substance corresponding to coprosterin.

HIPPOCOPROSTERIN: An allied substance isolated by Bondzynski and Humnicki and others from horse dung, which they regard as a further reduction product of cholesterin $C_{27}H_{50}O$. Gittelmacher-Wilenko has recently succeeded in isolating two hippocoprosterins. The α , which is easily soluble in 97% alcohol, crystallising in thin rhombic plates, and melting at 65° — $67^{\circ}C.$, and in benzol solution is optically inactive. The β only slightly soluble in alcohol, crystallising in needles, melting at $56^{\circ}C.$, and in benzol solution is slightly dextrorotatory.

ISOCHOLESTERIN: This term is applied to a somewhat ill-defined substance, or possibly a mixture of several isomeric or closely allied substances isolated by Schultze from wool-fat, in which it exists along with cholesterin in association with the higher fatty acids, and with which they are generally regarded as being combined, in the form of ethereal salts. It also has been isolated from the vernix caseosa.

Its empirical formula is said to be the same as that of cholesterin, $C_{27}H_{44}O$, from ether and acetone it crystallises in fine transparent needles, from strong alcohol it separates on cooling as a gummy mass, or on the addition of water in white flocculi, it melts at 137° — $138^{\circ}5C.$ Like cholesterin it adds a halogen molecule, it is optically active, being dextrorotatory, $\alpha^D = +60$ (7 grammes in 100cc. ether), a property which suggests that it may in some way be related to the so-called coprosterin. It gives the cholesterin colour reactions in a modified form.

PHYTOSTERIN: A generic term applied by Thoms to include the many substances isomeric with or allied to cholesterin, isolated from plants. They resemble cholesterin in empirical composition, $C_{27}H_{44}O$, in crystalline form from alcohol and from ether, in containing an alcoholic hydroxyl group, and in adding a halogen molecule. They differ from it and also

among themselves in melting point and in specific rotatory power, as will be seen in the following table :

Name.	Source.	M.P.	α_D	Observer.
Phytosterin	... Calabar bean	132 – 133	... – 34·2 CHCl. ₃ ...	Hesse
Do.	... Colchicum ... seeds	133	... – 32·7 CHCl. ₃ ...	Paschkis
Cholesterin	... Beans	... 131·5 – 132·5	... – 32·39 – 31·95	... Jacobson
Do.	... Vetch	... 134 – 135	... – 31·94 – 32·6	... Do.
Do.	... Peas	... 132 – 133	... – 30·53 – 30·41	... Do.
Do.	... Lupines	... 135·5 – 136·5	... – 34·43 – 32·95	... Do.
Phytosterin	... Lupine	... 136 – 137	... – 36·4 CHCl. ₃ ...	Schultze and Barbieri
Do.	... Pisum sativum	... 135	... —	... Likiernik
Paraphytosterin	... Phaseolus vulgaris	... 149 – 150	... – 44·1	... Do.
Caulosterin	... Lupine germs	158 – 159	... – 49·6 CHCl. ₃ ...	Schultze and Barbieri
Paracholesterin	... Aethalium septicum	... 134 – 134·5	... – 28·88 – 27·24	... Reinke and Rodewald
Hydrocarotin	... Carrot	... 136·5	... – 35	... Arnaud
Do.	... Do.	... 137·4	... – 37·4	... Reinitzer
Ergosterin	... Secale Cornutum	... 154	... – 44	... Tauret
Phytosterin	... Barley	... 137 – 138	... —	... Wallerstein
Sitosterin	... Rye & wheat...	137·5	... – 26·87 – 26·55	... Burian.
Parasitosterin	... Do.	127·5	... – 20·8	... Do.

The several members of this group of plant cholesterins present so little difference in the essential characters of melting point and rotatory power, that Ritter raised the question of their individuality and expressed the opinion that they all might very well be one and the same substance, in which varying impurity was responsible for such differences as had been noted. It might also be possible that many samples were mixtures of two different phytosterins and the variable properties due to their being associated in different proportions. Bömer had noted that the addition of cholesterin to phytosterin raised its melting point, then Windaus and Hauth definitely established the validity of the view of Ritter for the phytosterin isolated from the Calabar bean. From this substance they isolated two distinct bodies, one having all the properties of the sitosterin isolated by Burian and Ritter which was present to the extent of 80%, the other stigmasterin, $C_{30}H_{48}O$, which was capable of adding two molecules of a halogen.

THE BIOLOGICAL RELATIONS OF CHOLESTERIN.

The constant and wide distribution of substances of the cholesterin group, suggesting a constitutive significance for them, in the vegetable and animal cell, has already been referred to, and now it remains to examine the data on which this generalisation is founded, and further to bring together such observations as have been accomplished which will tend to elucidate, or at least suggest the lines for further attack of the interesting problems of the origin and fate of these substances in the living cell and of the rôle they therein sustain.

The general occurrence of a cholesterin-like substance in the vegetable cell was first suggested by the work of Beneke, who isolated from various seeds and germs a substance which was identified by Kolbe as cholesterin, but which was subsequently differentiated by Hesse who had obtained it from the Calabar bean and termed it Phytosterin. Since these fundamental investigations, it has been shown that phytosterins, the variability of which, as already indicated, depends in all probability on the admixture of a cholesterin isomer, with variable quantities of other bodies of different molecular weight, exist in members of the vegetable series from the bacteria upwards. Thus they have been isolated from the fatty constituents of various bacteria, from the myxomycetes, from various moulds and algæ, from the higher fungi, and from the seeds, leaves, tubers, and stems of large numbers of the higher plants. A distribution which could doubtless be extended by further investigation, but which already renders it highly probable that phytosterin is a constitutive element of the plant cell.

Recalling what has been previously said of the probable chemical relations of cholesterin and its isomers, that they apparently belong to the complex terpenes (sesquiterpenes), other members of which series as well as the simpler members of the same organic group, are, as products of organic nature, derived entirely from the vegetable kingdom, the general occurrence of phytosterin in the plant cell is perhaps less striking than is its similar relation to the animal cell, and on physiological grounds Tschirsch regards phytosterin as a normal constituent of all

vegetable protoplasm, and probably the mother substance of the closely related coniferous resins.

The occurrence of cholesterin and its congeners in members of the zoological series is less well known, though its distribution in the various tissues of the human being and some of the higher animals, has been much more completely established than is the case with the various tissues of the vegetable series.

In a microscopically invisible (dissolved or suspended) and physiological form, cholesterin is a normal constituent of the bile of all animals (except the *Scymnus borealis*, Hammarsten), it is a prominent constituent of all nervous tissue and also of the red and white corpuscles of blood and of the blood plasma, of all animals. In less amounts, it occurs in all normal cellular tissues, also in the cuticle of the skin and all keratinoid substances, hairs, feathers, hoof, etc., and in the fatty secretions of the cutaneous glands, sebaceum, vernix caseosa, dermoid cyst contents, and in the fat of sheep's wool (Lanolin). Occasionally its existence as a physiological product is indicated by its occurrence in a visible crystalline form, as in the cortical cells of the suprarenal capsule, and occasionally in the liver cells.

As a phenomenon of pathological processes of a retrograde type, cholesterin occurs in a visible crystalline form, in transudates and exudates—serous, hæmorrhagic, and purulent,—in hæmatomata, in mucous, sebaceous, and degeneration cysts, in morbid and to a less extent in normal secretions of mucous membranes, in the necrotic areas of atheromatous nodules, in the caseous material of tuberculous or syphilitic origin, in the degenerate and necrotic portions of neoplastic tissue, carcinomata in particular, and in gall-stones. In brief, cholesterin in a visible crystalline form is of usual occurrence wherever tissue elements of which it is a constituent are undergoing dissolution.

Realising the possibility of the occurrence of substances isomeric with or allied to cholesterin and of substances which might originate from it by oxidative processes in the tissues, it appeared that some useful purpose might be served by the examination of the cholesterin extract from various tissues as to the identity of the substances obtained, and, in view of its very definite behaviour towards inorganic solvents, it appeared equally

important to endeavour to elucidate the particular manner of its association in the tissues. It is towards these points that such of my own observations as can be dealt with in this section, have been directed, and according to the following method :—

A definite weight of fresh tissue, finely minced, ground into a pulp with clean sand (washed and extracted), is mixed with twice its volume of strong alcohol (98%) and after standing a few hours, is filtered through fine linen on the pump, the residue dried in a vacuum desiccator, the filtrate evaporated on the water bath and its residue added to that in the desiccator. In other cases dehydration was brought about by the use of plaster of Paris (Rosenheim) or by anhydrous sodium sulphate (Bünz). The dry, finely divided material is then extracted with ether in a Soxhlet or by repeated digestion. The ethereal extract divided into two equal parts, A and B, is evaporated to a small bulk, to each is added about 6 times its volume of dry acetone, previously cooled to 0°C. or below, and vigorously stirred or shaken to cause the precipitated lecithin to conglomerate, the ether-acetone extract containing the bulk of the cholesterin is poured off, the lecithin residue dissolved in a little ether and reprecipitated by cold acetone, this second ether-acetone extract is added to the first. Then, where a quantitative estimate of the cholesterin content of the tissue is required, the combined extracts from A are evaporated almost to dryness, dissolved in about 100cc. of alcohol on the water-bath and sodium ethylate (8 grm. sodium in 160cc. alcohol 99%) is added with constant stirring, and the mixture evaporated to dryness, to the dried residue about 100 grammes of NaCl is added and about 200cc. of water, the mixture well stirred, is again evaporated to dryness, and, further dried in the vacuum desiccator, and then extracted with ether in a Soxhlet's apparatus, the ether is distilled off, the residue treated with hot alcohol, diluted with water, and allowed to cool, the cholesterin which thus crystallises out is collected on a filter, washed with water, dried and weighed. The lecithin residue is then similarly treated with sodium-ethylate, etc., and any further cholesterin obtained added to the former. This precaution is soon found to be unnecessary, providing extraction with acetone has been thoroughly performed.

In the other portion, B, the ether-acetone extract is allowed to evaporate spontaneously, and as crystals appear they are filtered off, recrystallised from various solvents until of constant melting point, and the different crops compared one with the other. In this way it was hoped to detect the occurrence of allied substances by variations in melting point, and when sufficient material of constant melting point was obtained its optical activity was examined and its specific rotation determined.

Identity of Cholesterin from various sources: The cholesterin extracted, according to the method described, from brain, blood,

and gall-stones of the human subject proved by the coincidence of melting point and specific rotatory power to be identical. That, similarly extracted, from normal liver, spleen, lymphatic glands (ox), bile, fæces, from atheromatous nodules of the aorta, a peculiar type of hepatic cirrhosis, an ischæmic infarct of the spleen, and from the fluid of an old hæmorrhagic pleural effusion, gave melting points ranging within 144°C. and 146°C. , from which the identity of the cholesterin from these various sources with that of the gall-stone, may also be regarded as established. In no case was it possible to isolate any substance which could be regarded as a product of the oxidation of cholesterin, such being particularly sought after in the blood and in the liver. The facility with which cholesterin undergoes some degree of oxidation (*vide ante*) seemed to render it probable that such products would be met with, but so far as my own observations have proceeded this has not proved to be the case. Lifschültz, however, by a spectroscopic method, the significance of which it is difficult to estimate, believes that he has demonstrated such oxidation products (oxycholesterin, $\text{C}_{26}\text{H}_{42}(\text{OH})_2$ and its ether-like predecessor, $[\text{C}_{26}\text{H}_{43}]_2\text{O}$, *sic*) in wool-fat and in the ethereal extract of bone marrow and of blood. In the former Lifschültz premises that the cholesteryl esters, in which combination cholesterin is generally believed to exist in wool-fat, are hydrolysed by the potash salts in the sweat and the free cholesterin exposed on the surface of the fleece to the air and sunlight undergoes oxidation. It would appear *a priori* that if such oxidation products do naturally occur, wool-fat would be, above all others, the material in which to find them, and here a possibility at once suggests itself that the indefinite substance ischolesterin may be in some way related to such products.

Physico-chemical relations of Cholesterin in the Tissues: It has already been indicated that with few exceptions, the cholesterin which is a constitutive element of the normal cell and of the tissue fluids occurs in a microscopically invisible form, either in solution or suspension: while as a phenomenon of many pathological processes it appears in a definite crystalline form, which, particularly in the case of fluids, may be obvious to the

unaided eye, and in the majority of cases the crystals on microscopic examination have the characteristic form of the rhombic plate. Further, it is a matter of common observation that when normal tissues, particularly nervous tissues, have been retained for a long time in alcohol, there gradually separates out from the alcohol a crystalline deposit, which with few recrystallisations from hot alcohol can be shown to be pure cholesterin.

In view of these facts and of the known solubility relations of cholesterin it becomes of considerable interest to determine in what particular associations, if any, cholesterin exists in the cell-protoplasm and in the tissue fluids.

All observers from the earliest are agreed that from such material as nervous tissue or blood, it is possible by simple methods of extraction and fractional recrystallisation to obtain a certain percentage of the cholesterin in a free state, whilst the remainder according to the methods of the older observers, only obtainable after saponification with alcoholic potash, was generally believed to exist in some sort of combination. From tissues containing fat or from fatty secretions—wool-fat, vernix caseosa, dermoid cyst contents—and from blood serum it was found impossible to obtain free cholesterin without saponification, or if possible the amount obtainable was quite a small fraction of the total cholesterin content. In such cases the cholesterin was regarded as existing in combination with fatty acids as esters. Hartmann, and later Schultze, from the investigations of wool-fat, concluded that the cholesterin and the isocholesterin exist in a free state but also and chiefly in ethereal combination with the higher fatty acids and oleic acid, and possibly also with acetic and butyric acids.

Liebreich, using the Liebermann-Burchard reaction and the miscibility with water (“lanolisieren”) as criteria of cholesteryl esters, confirmed these observations, and further found that the esters were associated with keratinised structures, and were not necessarily formed in sebaceous glands, but might be formed within epidermic cells. He ascertained their existence in vernix caseosa, tortoiseshell, horn, whalebone, quills of porcupine and hedgehog, hoof of horse, feathers, etc. Ruppel also regarded the cholesterin of vernix caseosa as being in part in ethereal

combination with the higher fatty acids, and quite recently Salkowski has isolated from the epidermic scales desquamated from a case of dermatitis exfoliativa, a substance which he regards as cholesteryl palmitate.

Baumstark, who was unable to extract the whole of the cholesterin from brain without saponification, concluded, in view of Schultze's observations, that it existed in part as cholesteryl oleate, although he was unable to isolate any body having the properties of the synthetic ester.

From blood, Bordet isolated free cholesterin, and from the serum a substance which he regarded as being of definite composition, and which he termed Serolin; in 1852 Gobley explained this serolin as a mixture of fat, cholesterin and albumen.

It is, however, by the investigations of Hürthle on blood serum that the existence of the ethereal salts of cholesterin and fatty acids in the tissues is almost entirely substantiated. This observer, by fractional crystallisation with alcohol, obtained from the blood serum of the dog, pig, goat, ox and horse, crystalline substances of which, one had all the properties of the synthetic cholesteryl oleate, and another similarly corresponded with the synthetic cholesteryl palmitate. The oleate from different animals curiously gave different melting points, that from the horse and ox $43^{\circ}\text{C}.$, from the dog $41^{\circ}\text{C}.$, from the pig $45^{\circ}\text{C}.$, and, another unusual phenomenon he noted, without comment, was that recrystallisation of the initial crystals led to a progressive lowering of the melting point from $46^{\circ}\text{C}.$ to $41^{\circ}\text{C}.$

Since these observations it has been generally accepted that where cholesterin exists in association with fat and cannot be separated except by saponification it is present in the form of ethereal salts, and Adami and Aschoff, on the basis of the work of Lehmann, have furthered this view by setting up the phenomenon of anisotropism as a criterion for the existence of cholesteryl esters (or cholin oleate). Faust and Tallquist have isolated from the *Bothriocephalus latus*, and from human gastric mucous membrane, pancreas, and from a carcinoma of the stomach cholesterin which was apparently in ester-like combination. Cholesteryl oleate has been isolated from chylous ascitic

fluid by Wolff, and from a specimen of the large white kidney by Panzer. The cholesterin in the bile, also according to Aschoff, exists in ethereal combination with fatty acids.

My own observations have not, however, enabled me to confirm the occurrence of the true cholesteryl esters in any of the tissues or fluids investigated, including blood serum (ox).

From nervous tissue (brain) it was possible to extract the whole of the cholesterin in a free state without resort to saponification, a result which has also been attained by Bünz and by Tebb, and which was already suggested by Gamgee. From red blood corpuscles (human), as was already established by Wooldridge, and also from bile (human) cholesterin could similarly be wholly extracted. In these particular cases the cholesterin appeared to be invariably associated with lecithin, but the association, as shown by the method of separation, was probably entirely of a physical kind. From ox-serum—employing the method already described, but with this modification, that after treating the ethereal extract with acetone and filtering, about twice the volume of 97% alcohol was added and the mixture allowed to evaporate spontaneously—there was first obtained a small crop of crystals which on two recrystallisations from hot alcohol had a melting point of $144^{\circ}\text{C}.$; three further crops collected had melting points of $109^{\circ}\text{C}.$, $68^{\circ}\text{C}.$, and $45^{\circ}\text{C}.$, after each had been twice recrystallised; the addition of cholesterin to each one at once raised the melting point, and on treating the lowest with sodium carbonate in boiling alcohol crystals were obtained which had a melting point of $118^{\circ}\text{C}.$, and since the synthetic cholesteryl oleate is not hydrolysed by this procedure, it appeared that in all probability the crystals were mixtures of cholesterin and fat (probably fatty acid) and not true esters. From liver, analogous results were obtained, the ethereal extract yielding a small fraction of free cholesterin and needle-shaped crystals of varying melting point, and which showed very clearly the myelin reaction (*lanolisieren* of Liebreich) with warm water. Since the work of Hürthle, the occurrence of cholesterin in a free state in the blood serum has also been established by Letsche and by Hepner, but both these observers believe that the remaining cholesterin is in combination with

fatty acids in the form of esters. From the following pathological products the cholesterin was obtained at once in a free state, gall-stones, atheroma of the aorta, hepatic cirrhosis with visible areas of crystalline material, kindly placed at my disposal by Prof. Lorrain Smith, fluid from a case of hæmorrhagic effusion into the pleura of some duration (described by the late Dr. Harris). In all these cases the cholesterin had assumed a visible crystalline form, and appeared, from the facility with which it was purified to its proper melting point, that it probably existed in a free state.

So far as these observations have proceeded they seem to show that cholesterin exists in the cell protoplasm, in the blood serum, and probably also in fat in physical association with substances which render it miscible with water, and capable of being distributed in an emulsified or even colloidal condition, rather than in chemical combination with fatty acids or other substances.

In addition to the mixtures of cholesterin with fatty acids, soaps and to a less extent neutral fats, which, as already described, have this property, it is a much more pronounced property of mixtures of cholesterin and lecithin. Equal weights of cholesterin and lecithin dissolved in ether or any mutual solvent, give on evaporation of the solvent a transparent, yellowish, resinous-looking mass which can be rubbed with a little warm water into a creamy emulsion and then further diluted with water until it has the appearance and consistency of milk; such an emulsion or colloidal solution in water I have kept for three months without it showing any disposition to the separation of the cholesterin.

Cholesterin being regarded as a constitutive element of the normal cell, it may be premised that in such it is physically associated with lecithin, the mixture existing in a colloidal condition. In blood serum, in the fat of the liver, and in the fatty secretions of the skin, the cholesterin, which I regard as here being of very different significance, namely, as a product of cell dissolution, becomes associated with fats, fatty acids, and soaps or whatever combination of these is existent, and by them is maintained in a colloidal state to its excretion from the body.

With this conception of the relations of cholesterin in the normal tissues, the explanation of its appearance in a free crystalline form as a phenomenon of various retrograde pathological processes is at hand. Cholesterin by its chemical inertness is a substance of relatively great stability, while lecithin readily undergoes dissolution; in any retrograde process then which involves the cell protoplasm, the lecithin being readily broken up, the more stable cholesterin unable to maintain its colloidal state, unless there is present fatty acids or their derivatives, assumes a crystalline form. In brief, I would regard the visible cholesterin of pathological processes not as a product of any mysterious and subtle disintegration of the proteid or lecithin molecule, but simply as that which normally was present in an invisible form in the tissues and which, from alteration in its physical environment, has fallen out of solution.

The observations of certain other investigators are, however, in direct contradiction to this view. Carbonne is of opinion that not only fatty acids and neutral fats but cholesterin also originate as products of the decomposition of lecithin, and Waldvogel also claims to have established a similar relation, as is indicated in the following table, which gives the result of the autolysis of lecithin by sterile liver juice :—

Duration of autolysis in days.		Lecithin.	Fatty acids.	Fats.	Cholesterin.			
0	...	11·8	...	0·52	...	0·06	...	0·07
13	...	6·82	...	1·80	...	0·96	...	1·80
44	...	1·06	...	3·74	...	3·61	...	5·41

In pathological liver tissue this observer also determined the occurrence of increased quantities of these substances as compared with the normal organ; an extreme example from his analyses is the following, which gives the percentage of these substances in dry liver tissue from a normal organ and from a case of acute poisoning :—

	Fatty acids.		Neutral fats.		Cholesterin.
Normal	1·04	...	2·44	...	0·42
Pathological ...	7·73	...	7·95	...	24·46

My own observations on the relation of cholesterin to autolysis, although few, have not afforded results at all comparable with those of Waldvogel, nor, so far as I am aware, has any other observer given them confirmation.

I. 600 grammes of normal human liver, which by control extractions was found to contain 0·038 % of cholesterin, was allowed to undergo aseptic autolysis (toluol method) for 42 days at 37°C., at the end of this period an estimation of the cholesterin content gave 0·0372 %.

2. Estimations of the cholesterin content of the spleen pulp (human) and of necrosed spleen pulp from the same organ (a large ischæmic infarct) gave practically the same percentage in the normal and the morbid :—

Spleen pulp, 0·64 %.

Infarct, 0·58 %.

Results which would seem to indicate that the disintegration of cell protoplasm is not associated with any increase in the absolute cholesterin content, as is maintained by Carbone and Waldvogel. The seeming abundance of the crystalline cholesterin in certain pathological products, which in itself might suggest a new formation of cholesterin, is generally more apparent than real—thus in the specimen of pleural fluid in which the cholesterin crystals were so abundant as to give it the appearance of “silver paint,” the actual percentage found was 0·052, which is somewhat less than that of normal blood—and even in such cases as where there is an actual increase in the cholesterin content over and above the normal, this may be readily explained by the removal of other products of cell dissolution and a concentration of the cholesterin. The existence of cholesterin as a constituent of keratinoid substances would appear to be in accordance with this view, it remaining unchanged and perhaps relatively increased in amount with the process of keratinisation.

On such grounds, I believe, cholesterin may be regarded as a constitutive element of the normal cell, and of such stability that it not uncommonly remains as a visible indication of previous cell dissolution.

The mode of origin, the fate and the significance of cholesterin in the animal cell : These problems, which have been the subject of diverse hypotheses generated under the influence of a doctrine which modern research is proving to be ill-founded and

erroneous, namely, that whereas synthetic phenomena are essential characteristics of vegetable protoplasm, destructive phenomena are the dominant features of the animal cell, and with cholesterin as with other complex constituents of the animal organism, the origin has been sought, either in some retrograde change of apparently still more complex bodies, or in the direct transference of the substance from the vegetable to the animal cell. Both these views have been expressed in explanation of the occurrence of cholesterin in the animal cell, the former propounded by Hoppe-Seyler is generally accepted, and regards cholesterin as a cleavage product constantly formed in the metabolic changes of the living cell, and accordingly an invariable constituent of both of the animal and vegetable cell. Such a hypothesis, acceptable in the absence of any knowledge of the general occurrence of synthetic processes in the animal cell, is contrary to such knowledge as we possess of the constitution of the products of proteid, fat or carbohydrate dissolution, and it is difficult to reconcile with what we know of the metabolites in general.

That the cholesterin of the animal cell is entirely derived from that taken into the organism with vegetable food has been seriously advanced, but is quite unsupported by any known facts.

As the synthetic capabilities of the animal cell become more definitely established a substance of the constitutional relations of cholesterin, which in the animal organism occupies a class alone, with perhaps inosite as its nearest analogue, is more easily conceivable as a product of such processes than of the disintegration of any other known constituent.

Cholesterin is continually being lost to the organism, and it would appear that this is in immediate sequential relation to cell dissolution. It has already been premised that the liberation of cholesterin which occurs in pathological cytolysis is not uncommonly associated with the deposition of cholesterin *in situ* in a crystalline form, when its resistance to disintegratory processes becomes manifest by its persistence for long periods, and further, in those situations where the retrograde processes which gave the cholesterin liberty are succeeded by reactive reparative phenomena, by the not unusual feature of the

cholesterin crystals being invested by giant cells, showing that the organism is dealing with them as it would with any inert resisting body.

Under physiological conditions the processes of cell dissolution are, I believe, equally with the pathological, associated with the liberation of cholesterin, and yet it rarely, if ever, assumes the crystalline form, but continues to retain its colloidal state either as a result of the non-involvement of the lecithin in the disintegratory process or, what appears more probable, of its becoming associated with neutral fats, fatty acids, and may be soaps, which themselves may, wholly or in part, be products of the splitting of the lecithin molecule, and in such combination it is excreted from the organism. On the surface of the body where cell dissolution of a particular type—keratinisation—is a continuous process, cholesterin associated with the fatty secretions of the sebaceous glands is a prominent constituent of the oily secretions of the skin, and that its origin is from the desquamated cuticular layers rather than from the sebaceous glands themselves is shown by the researches of Liebreich. From mucous membranes where the phenomenon of cell dissolution also occurs, but to a less degree, cholesterin, as shown by its presence in the bronchial secretion, is a constant but insignificant constituent, and doubtless also from the gastro-intestinal and other mucous membranes cholesterin will occur in amount proportional to the degree of cell dissolution.

It is, however, the fate of the cholesterin liberated within the organism, in the normal cytolytic processes, that calls for consideration. While it is possible that cytolysis is, in some measure, a physiological phenomenon of every tissue of the organism, continuous dissolution with continuous regeneration is a striking feature of the life history of the red blood corpuscle, an element which, next to the nervous tissue, is richest in cholesterin. The fate of the cholesterin liberated in this process is recondite, but in the absence of any evidence to the contrary it may be regarded as constituting the cholesterin of the blood plasma, where it has become associated with fatty acids and their derivatives, and, may be, in part, also still retains its association with lecithin. The abnormally large amounts of cholesterin

which have been shown to exist in the blood plasma in certain severe types of diabetes mellitus (Fischer and others) is perhaps an expression of rapid cell dissolution which is a phenomenon of this morbid state.

The ultimate destiny of this cholesterin, no longer a protoplasmic constituent, would seem to be that it is excreted by the liver, although this view of the origin of the bile cholesterin has been largely overshadowed by the dominant views of Naunyn that this latter is almost exclusively of mucous membrane origin.

In the bile, cholesterin, it would appear from my own analyses of human bile from a gall-bladder fistula, is still associated with lecithin, and held in a colloidal state by that substance, aided by the sodium salts of fatty acids, the bile acids in particular; an association which, from the observations of Gérard, may be destroyed by bacterial activity and lead to the deposition of cholesterin in a crystalline form.

Excreted with the bile into the intestine, cholesterin may be resorbed in combination with fatty substances to some small extent, but from direct experimentation (Naunyn, Thomas) there is no evidence to regard it as a significant phenomenon, and, together with that derived from the dissolution of the cells of the gastro-intestinal mucous membrane, it is excreted from the body with the fæces, in which, according to the investigations of Bondzynski and Müller, it may have undergone an apparent reduction.

In this connection it is interesting to record that the extraction of 100 grammes of dry fæces from an individual in whom there was complete stenosis of the common bile duct, failed to yield either cholesterin or coprosterin in sufficient quantity to enable me to recognise them.

Summary:—As a constituent of the living cell and as a product of its synthetic activity, cholesterin, associated with lecithin in a colloidal state, may be regarded as constituting—as its characteristic inertness would lead one to premise—in part, at least, that relatively stable structural protoplasmic reticulum—the spongioplasm—in the meshes of which is contained the labile hyaloplasm. Such is the hypothesis which the results of my own investigations appear to suggest, and such appears to more

closely accord with the diverse facts as have been established by the work of others. With the dissolution of the cell—normal or morbid—the cholesterin, the least destructible of the several constituents, liberated from such physical association as maintained it in colloid state, either assumes a crystalline form, or, acquiring new association with fatty acids and their derivatives (glyceryl esters—salts), is still maintained in a colloidal state, and, being conveyed to the liver, is excreted thence into the bile and so from the organism. Much investigation may be necessary to the completion of this roughly-drafted hypothesis, but it is in this direction, I believe, that the solution of the problems of the origin and significance of cholesterin is to be sought.

The rôle of cholesterin in the cell :—The peculiar stability of cholesterin would appear to preclude it from any significant part in the complex of chemical changes which characterise living protoplasm, but there are many indications that this substance may, in virtue of its physical properties, and particularly that which may be designated its adsorptive power, have a very profound significance for the cell economy.

The peculiar relations which obtain between cholesterin and water, alcohol, and the fatty acids, in particular, which have already been considered, appear to be analogous to its relations to certain other substances.

In a series of investigations on the physico-chemical basis of plasmolysis and intravital staining, Overton determined that those substances which are able to penetrate into the living cell have in common the property of being fat soluble, and of being soluble in cholesterin, lecithin, and also in such other lipoids as cerebrin and protagon, whilst those substances which are unable to penetrate the living cell except in some indirect manner have not this property. Overton accordingly formulated the hypothesis that cholesterin, lecithin, and other similar lipoids are essential constituents of the cell protoplasm, varying physically and possibly chemically within certain limits with different orders of cells, and that these lipoids constitute by peripheral concentration a semi-permeable membrane investing the cell. According to this observer the substances which diffuse into and out of the cell most rapidly are the monohydric alcohols,

aldehydes, ketones, aldoximes, ketoximes, mono- di- and tri-halogen derivatives of the hydro-carbons, nitro-alkyls, alkyl cyanides, the neutral esters of inorganic and many organic acids, aniline, etc.; those which possess this property to a less extent are the dihydric alcohols, and the amido compounds of the monocarboxylic acids; to a still less extent, glycerine, urea, thiourea, and erythritol; and to a scarcely perceptible degree, the hexahydric alcohols, the hexoses, amidoacids and the neutral salts of inorganic acids.

Those aniline dyes which possess the property of intravital stains—neutral red, methylene blue, toluidine blue, nile blue, safranin,—are lipoid soluble, whilst other dyes which do not possess this property have not this particular solubility relation.

It is interesting to note that with intravital staining, the cell protoplasm is not uniformly coloured, but that certain granules, which, according to Höber correspond with the “ granula ” of Altmann, are stained most intensely and would thus appear to have a lipoid constitution; as cholesterin is a probable constituent this phenomenon affords some support for the hypothesis previously formulated.

Whether Overton's conception of the lipoid cell membrane be accepted or not, it must be conceded that this observer has accumulated a large amount of evidence to show that the living cell will take up either by osmosis or adsorption substances which *in vitro* are soluble in (or adsorbable by) cholesterin, lecithin and other less definitely constituted lipoids.

In the phenomenon of hæmolysis which has attracted considerable attention during recent years, cholesterin appears to play a significant rôle, and in a fashion analogous to that which it sustains in the preceding phenomena.

In 1901 Ransom, investigating the mode of action of saponin on blood, found that red corpuscles washed entirely free from blood serum were much more susceptible to the hæmolytic action of saponin than were those with which serum was still associated; and he found that the constituent of the serum which interfered with the hæmolytic action of the saponin was contained in its ethereal extract and was cholesterin, lecithin, which also combined with the saponin, having no effect on its toxicity for the red

corpuscles. He concluded that the toxic action of saponin depended on the affinity or solubility relation which obtained between this substance and the cholesterin-lecithin constituent of the cell, and, further, that the existence of extra-cellular cholesterin might, within certain limits, be a means of defence against the toxic action of saponin and members of the saponin group, but not against such other hæmolysins of vegetable origin as phallin and crotin nor against hæmolytic alien sera, on which he found cholesterin to be without effect. Noguchi further established that cholesterin is capable of neutralising the hæmolytic action of agaricin, saponin, and tetanolysin, and that lecithin has no such effect.

Flexner and Noguchi, working with cobra venom, found that red corpuscles washed free from blood serum were agglutinated by this venom, but only in the presence of blood serum did they undergo dissolution, from which they concluded that the venom-hæmolysin is of the nature of an amboceptor (or perhaps more accurately an amboceptor-complement complex) which is activated by some substance in the blood serum.

Kyes, confirming these observations, succeeded in showing that lecithin is the activating substance for the amboceptor of cobra venom, and he regarded the combination of lecithin with cobra venom as being of a chemical nature, as he was able to prepare and isolate the lecithade of cobra venom and also of other venoms.

In certain species it was found that the red corpuscles, even after being washed free of serum were dissolved by cobra venom, and in such, according to Kyes and Sachs, the cobra venom amboceptor is activated by the lecithin of the corpuscle itself, which accordingly must be more loosely combined than in those corpuscles which are resistant when washed free from serum.

Koeppé, Peskind, Van de Velde and others have pointed out that the hæmolytic activity of such substances as chloroform, ether, bile salts, amyl alcohol, etc., probably depends on their being solvents of cholesterin and lecithin.

Pascucci, employing silk membranes permeated with mixtures of cholesterin and lecithin in proportions varying from 1:1 to 5:1, found these were rendered permeable to solutions of

hæmoglobin and cochineal in normal saline, by such hæmolytic substances as saponin, solanin, cobra venom, tetanus toxin, and the more rapidly the less cholesterin they contained. He further confirmed that the addition of lecithin to the hæmolysins had no effect, whilst the addition of cholesterin sufficed to neutralise their activity; and he suggested that the varying resistance of washed red corpuscles to cobra venom might be explained by the varying quantitative relations of lecithin and cholesterin in the corpuscles.

Madsen and Noguchi, investigating the degree of dissociation of the cholesterin+saponin combination by measuring the hæmolytic activity of various cholesterin+saponin mixtures, found that the formula representing the diphtheria toxin+anti-toxin mixtures agreed most closely with the observed values—

$$\frac{1}{T_0} \left[N \frac{1}{T} p - \left(\frac{1}{T} - \frac{1}{T_0} \right) \right] = K_1 \left(\frac{1}{T} - \frac{1}{T_0} \right)^{\frac{2}{3}}$$

Where T =hæmolytic activity, N =quantity of cholesterin, $\frac{1}{p}$ =equivalent number of cholesterin to saponin.

On evaporating to dryness a cholesterin+saponin mixture inactive to blood, they obtained a pulverisable mass which frothed into solution on the addition of water. But as the cholesterin could readily be isolated by chloroform they observed that the combination must be a very loose one.

In these several phenomena in which cholesterin is concerned, the manner of its action has yet to be explained. It may be premised that cholesterin acts purely physically as by adsorption a property which it possesses in a high degree, or its action may on the other hand be of a chemical nature, as Ransom and others suggest.

With the view of elucidating this problem Abderhalden and Le Count have examined, comparatively, the effect of cholesterin from various sources and of a large series of its derivatives on the hæmolytic activity of cobra venom, tetanus toxin, saponin, solanin and vibriolysin. Early in their investigations, from the results obtained with a limited number of cholesterin derivatives and a few hæmolytic substances, the conclusion appeared inevitable that the action of cholesterin depended on the integrity of its hydroxyl group and to less extent on the integrity of its

unsaturated condition; but the results of more extensive experiments showed that such definite conclusions were premature. Hausmann, with a similar object in view examined the comparative effects of a large series of cholesterin derivatives in the hæmolytic activity of saponin, and concluded from the results obtained that the antitoxic action of cholesterin was abolished by substitution of the hydroxyl group, and that it was weakened, although not abolished, by the saturation of the molecule.

Conclusions identical with those which Abderhalden and Le Count had by further investigation been caused to seriously modify.

It would thus appear from the results of such investigations as have been concerned, immediately or remotely, with cholesterin as a cell constituent, that this substance may be of fundamental importance in the physico-chemical processes of the cell, exerting a profound influence on the ingress and egress of substances which have particular solubility relations, either in virtue of its adsorptive power or in some other as yet more recondite manner which may be associated with some special features of its molecular constitution.

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NOTES ON A CASE OF PHOSPHORUS POISONING,
WITH SOME OBSERVATIONS ON THE AMINO-
ACID EXCRETION.

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ON September 16th, 1906, a non-pregnant woman, 26 years old, swallowed, with suicidal intent, the heads of a box of 'England's Glory Matches.' The quantity of yellow phosphorus present in a similar box was 0.0619 grammes.¹

The next day she vomited frequently, and took four Beecham's pills in the hope of 'passing' the poison.

On the morning of the 16th, her bowels were opened several times, but she continued to vomit, and was admitted to the Royal Infirmary. She complained only of the vomiting and did not have any pain either then, or at any subsequent period of her illness. The temperature was normal. The tongue was tremulous, moist, and covered with a yellow fur. The skin of the abdomen and the sclerotics were slightly but distinctly yellow in colour. Her pulse was 80 per minute, irregular in time, and of low tension. The cardiac apex beat was in the 5th space, one inch external to the nipple line, and there was an apical systolic murmur conducted into the axilla. This was

1. This was determined from the weight of the scrapings of the matches in a box and from the percentage composition (kindly supplied by the makers) of the paste used in their manufacture.

probably due to rheumatic fever from which she had repeatedly suffered. There was no symptomatic or physical evidence of cardiac failure. The abdomen, which was not distended, was uniformly tender on pressure; it moved with respiration. The hepatic dulness on percussion extended from the 6th rib in the nipple line to the costal margin. The patient complained of pain when the dull area was pressed upon or percussed. The spleen was not enlarged.

There was retention of urine.

The patient was given ℥ xl. of French turpentine every six hours for the first day, and subsequently ℥ xl. of sanitas four times a day.

She vomited twice on the day of admission. No phosphorus was detected on distillation of this vomit. On September 17th she vomited once—but not subsequently. On September 19th the jaundice was deeper and had spread to the rest of the body. The liver extended to 1 inch below the costal margin. On September 21st the jaundice was still more marked, and the uniformly enlarged liver extended down to the level of the umbilicus; it was very tender and soft.

On the 22nd the liver was slightly less in size, its lower edge being 1 inch above the level of the umbilicus. The pulse was now regular in frequency. The jaundice was slightly less marked. Examination of the blood showed 5,500,000 red corpuscles, 75 per cent. of hæmoglobin, and 4,480 white corpuscles per cb.mm. On September 24th, the lower edge of the liver was only 1 inch below the costal margin, and the jaundice was still less.

On October 1st the abdominal tenderness had disappeared, and a catheter was no longer required.

On October 4th the jaundice was nearly gone, and the liver was no longer palpable; its lower edge as determined by percussion extended to the costal margin.

Two days later the patient went home, at her own request. She was quite well twenty-three days subsequently; she did not subsequently return, though requested to do so, and we failed to trace her.

The urine, drawn off by catheter shortly after admission, was

reddish brown in colour, s.g. 1034, and contained neither albumen, sugar nor blood. Determinations were made, day by day, of the total nitrogen, urea, ammonia, and purins, excreted.

Day.	Total nitrogen. gm.	Urea nitrogen. ¹ gm.	Ammonia. ¹ gm.	Purin nitrogen. gm.
3 ...	7·6375	... 7·034	... 3158	... 1560
4 ...	9·8751	... 9·101	... 3576	... 1842
5 ...	9·2064	... 8·410	... 4095	... 2730
6 ...	9·2840	... 8·192	... 2565	... 1522
7 ...	9·9584	... 8·705	... 8736	... 1640
8 ...	12·6112	... 11·672	... 5376	... 1328
9 lost.				
10 ...	12·4684	... 10·965	... 7856	... 1400
11 ...	10·8528	... 9·763	... 5236	... 1520
12 ...	11·6325	... 10·807	... 6585	... 1324
13 ...	10·0005	... 9·143	... 6174	... 1410
14 ...	10·1908	... 9·216	... 6623	... 0900
15 ...	10·0680	... 9·304	... 6697	... 1210

The diet was a weighed hospital low diet, with a constant quantity of fish.

The nitrogen output corresponded fairly well to the intake. The ammonia output was not high. The purin nitrogen was normal except for a slight increase on the fifth day. Hæmatoporphyrin, sarcolactic acid, and sugar were absent. Urobilin was found in considerable quantities during the third and fourth days, and in traces for the next three days. Bile-pigments were present for three days and then disappeared. Good reactions for indican were obtained during the first seven days.

Wohlgemuth² has shown that, experimentally, the urine of animals poisoned by phosphorus contains arginin in addition to the usual amino-acids, and has recorded a case in which that substance was present in the urine of a patient who died from phosphorus poisoning nine days after eating all the match-heads in a large box of matches. These facts lend additional interest to the observations of Wakeman³ upon the decreased quantity of arginin present in the hepatic cells in cases of

1. The estimations of the ammonia and urea were carried out by A. J. Taylor, M.P.S., dispenser to the Bristol Royal Infirmary.

2. Wohlgemuth, J. Zur kenntnis des Phosphorharns. Zeitschr. f. physiolog. Chemie. Bd. 44, Heft. 1, S., 75.

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experimental phosphorus poisoning when compared with healthy liver tissue.

It consequently seemed advisable to examine the urine of this patient for diamino-acids as well as for mon-amino-acids. Using the naphthalene-sulpho-chloride methods, glycocoll, tyrosin, and leucin were all identified. Leucin occurred in large amounts for three days, and in small amounts for the succeeding ten days. Small quantities were still demonstrable in the urine obtained twenty-three days after the patient left the Infirmary. Tyrosin occurred in smaller quantities. As the presence of these mon-amino-acids is now generally accepted as "proved" in cases of phosphorus poisoning, quantitative estimations were not undertaken. The urine was accumulated until six litres were obtained and this quantity was used for determination of arginin.

Method. After precipitation by the addition of excess of lead acetate, and removal of the lead by H_2S , the filtrate was evaporated at $40^\circ C$. in vacuo to a thin syrup. Ether was then added in order to remove substances which might interfere with subsequent stages. The ether was separated off, and an excess of phosphotungstic acid was added. This precipitate was treated according to the method of Wohlgemuth.¹ When the purins, etc., were removed, the addition of an alcoholic solution of picrolonic acid is followed by the appearance of crystals if arginin is present.

No arginin was present.

In view of the remarks of Wohlgemuth in connection with the stability of the nuclein of phosphorus livers, the urine was also examined for the presence of pentose.

*Method.*¹ 500 cc. of urine were evaporated on a waterbath down to 200 cc. 200 cc. of alcohol were then added. After standing for four hours the deposited urates and organic salts were filtered off, and the residue well washed with alcohol. The filtrates were evaporated to a thin syrup and an equal quantity of 99 per cent. alcohol was added. After standing for two hours, the solution was filtered, and di-phenyl-hydrazine

1. For some of the details connected with this method we wish to express our indebtedness to Dr. J. Wohlgemuth.

added to the filtrate. The solution was then warmed on the water bath for half an hour in order to get rid of the alcohol. When pentose is present the crystals deposited are collected twenty-four hours later, washed with 30 cc. of 30 per cent. alcohol, dried at 80°C. and weighed (1 gm. arabinose equals 1.4 gm. diphenyl-hydrazine). The method gives a yield of 99 to 99.8 per cent.

No pentose was present.

In looking over the clinical records of this case of phosphorus poisoning, it is seen that vomiting occurred on the second, third and fourth days after taking the match heads, and then ceased. The rapidity and extent of the alterations in the size of the liver were most striking. The liver was of normal size in the fourth day, it began to swell on the fifth, reached its maximum size on the seventh, when it extended down to the level of the umbilicus; it began to diminish in size on the eighth, and was of normal dimensions on the twentieth day. The change in the liver began, however, before any enlargement took place, for it was very tender on percussion in the second day, slight jaundice was already present, and leucin and tyrosin were demonstrable in the urine. The jaundice also attained its maximum on the seventh day, and then declined *pari passu* with the diminution in the size of the liver. It was a little odd that the jaundice began in the skin of the abdomen. Though the liver attained its normal size by the twentieth day, yet pathological changes were still going on, for leucin was demonstrable in small amounts in the urine on the forty-fifth day. The retention of urine was probably connected with the tenderness of the abdomen; it is a somewhat exceptional feature. The irregularity in the action of the heart was probably due to direct action of the phosphorus on the cardiac muscle.

The experimental evidence already accumulated suggests that we may exclude decreased oxygen supply to the tissues as a cause for the effects met with in phosphorus poisoning. There are, however, distinct signs of a diminished oxidative capacity of the tissue cells, and it may be taken that phosphorus acts directly on the cell protoplasm. It has a selective affinity for certain cells, especially those of the liver, kidneys, and heart.

This action has been chiefly studied in connection with hepatic cells, and appears to result in an excessive cleavage of albumin, with formation of amino-acids. The extent of this production determines—to some extent—our view of the oxidative capacities of the cells. On the one hand, the assimilative powers of the organism for the products of albumin cleavage are not destroyed, although they are unequal to dealing with a sudden liberation of large quantities of these substances. On the other hand, the assimilative powers may be so depressed that even small amounts of the liberated acids are not fully dealt with. Again, it is quite conceivable that a condition of marked destruction might coincide with one of deficient assimilation.

In this instance, as far as the acute manifestations were concerned, there was an explosive type of tissue destruction, the amino-acids being rapidly eliminated, followed by a rapid return to normal conditions. It illustrates the view that in phosphorus poisoning, the total assimilation powers for the albumin cleavage products are unimpaired though they are not able to deal with any extraordinary quantities. The absence of arginin from the urine of our case may be due to the fact that despite the severity of the earlier symptoms the later ones were less marked and the patient lived beyond the usual period of the severe cases. It is a matter for regret that we were unable to make further examinations of the urine at later dates—the patient was lost sight of and could not be traced—for although the immediate destruction of hepatic tissue appeared to cease, a consequential ‘inadequacy’ of the liver might have arisen.

CHOLESTEROL, FLUID CRYSTALS AND MYELIN FORMS.

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NUMEROUS observers have noticed in the tissues in various conditions globules closely resembling fat globules, but differing from these in staining but faintly with ordinary fat stains and in being anisotropic. Such a globule when examined with polarised light with crossed Nicols, presents the appearance of a bright globule divided into four quadrants by a black cross which has its arms parallel to the axes of the Nicols.*

In examining frozen sections of carcinomata and other tumours fixed in formalin it is common to find masses of fine acicular crystals. These may be either intra- or extra-cellular and they are often quite apart from any evident degeneration. On placing such a section on the warm stage and heating, the crystals melt at temperatures varying in different specimens into a group of globules closely resembling fat globules. On now cooling the specimen the globules become anisotropic. This distinguishes these crystals from ordinary fat crystals which do not give rise to anisotropic globules under these conditions. These anisotropic globules are persistent for a long time at room temperature but, in some cases, they undergo subsequent solidification. In some cases similar globules are found in the section without previous warming. I have also seen these globules in some cases of supposed fatty degeneration of the kidney and liver and in some other conditions. Normal formalin-fixed adrenals invariably show masses of crystals which become anisotropic globules on warming and subsequent cooling.

On treating a section containing these anisotropic globules

* N.B.—All anisotropic globules do not show this cross which depends on the internal structure of the globule but, in this paper, only those globules which have this characteristic are considered.

with 85 per cent. sulphuric acid the globules usually assume a brown or purple colour, the presence of cholesterol being thus indicated. If the section be stained with Nile blue and heated on the stage the globules sometimes become stained a deep blue colour. This indicates the presence of fatty acid. Sometimes, on the other hand, the globules are stained pink, indicating the absence of free acid.

Sometimes, along with the globules, cylindrical forms are seen which closely resemble the myelin forms seen on treating lecithin with water.

With the object of finding out the conditions under which such globules and myelin forms occur I have undertaken the following investigation. The histological results I shall leave for a future occasion, confining myself here to some observations on cholesterol and fatty acids.

MATERIALS USED IN THE INVESTIGATION.

Cholesterol. The cholesterol used in this investigation was prepared from gall stones and purified by recrystallisation from absolute alcohol until it showed a melting point of at least 145°C. If cholesterol with a lower melting point be used it is apt to lead to erroneous conclusions. Commercial cholesterol contains admixed fatty acids and requires a considerable amount of purification before it can be used. For one sample of cholesterol (and for samples of cholesterol bromide and cholesteryl chloride and oleate) I am indebted to Dr. Craven Moore; the others I prepared myself.

Of the cholesteryl esters I used chiefly the palmitate which is easily prepared pure by heating together cholesterol and palmityl chloride. I have also examined the chloride, formate, acetate, propionate, and oleate.

In connection with fluid crystals I examined for the purposes of comparison the substances p-azoxyanisol, p-azoxyphenetol, and the octyl and cetyl esters of p-azoxycinnamic acid. These are representatives of substances showing Lehmann's "flüssige Kristalle" as opposed to the "fliessende Kristalle" of the cholesteryl esters. These substances were obtained from Schuchard. The other chemicals were obtained from Kahlbaum.

The following fatty acids and their potassium salts were used :—

$C_{n-1}H_{2n-1}COOH$	Formic, Acetic, Propionic, Butyric, Isovaleric, Caproic, Caprylic, Nonylic, Lauric, Palmitic Stearic.
$C_{n-1}H_{2n-3}COOH$	Undecylenic, Oleic, Elaidic, Erucic.
$C_{n-1}H_{2n-5}COOH$	Linoleic.
$C_{n-1}H_{2n-2}OH.COOH$	Lactic.
$C_{n-1}H_{2n-3}(OH)_2COOH$	Dioxystearic.

I also made use of the neutral fats triolein, tripalmitin, tristearin, and mono- and di-palmitin (prepared from the corresponding chlorhydrin and sodium palmitate); also the ethyl, cetyl, phenyl, menthyl, and linaloyl palmitates prepared from the corresponding alcohols and palmityl chloride.

The microscope stage that I used was heated with water and so arranged that, by a series of stopcocks, either hot or cold water could be supplied to the stage, and the outflow from the stage could be made to pass at will through a vessel containing a gas regulator which regulated the temperature of the water bath from which the hot water was obtained. With this arrangement the temperature could be raised or lowered slowly or quickly and any temperature between 14° and $95^{\circ}C$.—corresponding to corrected temperatures of 15° — $79^{\circ}C$.—could be obtained and maintained for any length of time. The temperature of the preparation in the field of view was standardised by observing the melting points of various pure chemicals and comparing them with the melting points observed in capillary tubes. The stage was used in conjunction with polarised light. The temperatures given in this paper are Centigrade and, where the observations have been made on the stage, the necessary corrections have been made.

CHOLESTEROL.

I do not propose to consider in detail the characters of cholesterol and cholesteryl esters but only to give an account of certain observations which have been made during this investigation.

If some dry cholesterol be heated to 135° —*i.e.*, 10° below its melting point—between two cover glasses it softens and

becomes yellow and, at the same time, a sublimate appears on the upper cover glass in the form of rectangular plates. The sublimate gives the colour reaction with sulphuric acid. I have not investigated this substance any farther.

Cholesterol when heated to a temperature of 135° for three hours in a capillary tube becomes yellow and liquefies. This substance on cooling solidifies to a brown amorphous mass resembling resin which, under certain conditions, can be obtained in a partially crystalline condition. On heating it softens at a temperature below 100° and becomes perfectly clear and fluid at about 128° . This change in cholesterol does not occur if the melting point tube be closed even on heating for several days nor does it occur if the heating be carried out in a stream of CO_2 to 140° for 15 hours. If, on the other hand, the heating be carried out in a stream of air or oxygen the change is rapid, the change of colour in the case of oxygen being noticeable in 5—10 minutes. During the process the cholesterol gains in weight. This yellow substance is, therefore, an oxidation product of cholesterol. I have not investigated it any farther.

FLUID CRYSTALS.

Anisotropic globules are known to occur under certain conditions in some of the substances which are characterised by having a crystalline fluid phase. In this condition the substance is composed of crystals which are themselves fluid and the crystalline fluid may be extremely mobile or as viscous as glycerine. The solid crystals of the majority of such substances on being heated melt at a definite temperature into a turbid crystalline fluid which, on further heating, becomes clear and amorphous at a temperature which also is definite for each substance. The crystalline fluid phase is thus a stable condition between two temperatures which are fixed for each substance. Thus cholesteryl oleate crystallises in rhomboid plates which melt at 38° – 39° to a crystalline fluid which clears at 49° . On cooling, the fluid crystals appear at 45° and these are gradually replaced by the solid crystals on standing for some time at room temperature, solidification being complete after 12—18 hours. In this case then the crystalline fluid phase

is a stable condition between 39° and 49° and a metastable condition below 39° . We can represent the phases of cholesteryl oleate as follows :

CRYSTALLINE SOLID \rightleftharpoons CRYSTALLINE FLUID \rightleftharpoons AMORPHOUS FLUID.

In some cases, however, the conditions are somewhat different. In these cases, of which examples are cholesteryl chloride, formate, acetate, and palmitate, the solid substance melts directly into the amorphous fluid and the crystalline fluid phase exists as a metastable condition between two more or less definite temperatures below the melting point of the solid crystals.

Thus on heating cholesteryl palmitate it melts at 77° – 77.5° to an amorphous, slightly opalescent fluid which loses its opalescence at 80° . On cooling slowly the fluid becomes opalescent at 80° , fluid crystals appear at 76° , and solid crystals at 71° , in the form of radiating needles or prisms. If the crystalline fluid phase is kept for some time at a constant temperature the fluid crystals are gradually replaced by large solid tabular crystals. On heating the radiating masses of crystals obtained by cooling they change into the tabular stable form before melting. All these changes can be observed directly on the warm stage.

The phases of cholesteryl palmitate can be represented as follows :

CRYSTALLINE SOLID I. (PLATES)	\rightleftharpoons \rightleftharpoons	AMORPHOUS FLUID.
↑	↖	↓
CRYSTALLINE SOLID II. (NEEDLES)	←	CRYSTALLINE FLUID.

Similarly on cooling cholesteryl chloride which has been melted (M.P. 94°) very slowly the solid crystals may appear directly from the clear fluid. If it is cooled rapidly fluid crystals appear and are remarkably persistent lasting for several hours at room temperature and showing iridescent colours, but they are eventually replaced by solid crystals. On warming such a preparation the solid crystals appear more rapidly and spread in radiating masses through the crystalline fluid. If cooling take place moderately slowly as by placing the preparation on the stage at 79° and cooling slowly, fluid crystals appear

at 64° and remain to about 52° , when the solid crystals appear. If the crystalline fluid phase is heated above 64° the fluid clears at this point and solid crystals appear in the clear fluid. The acetate and formate behave in a similar way. All the cholesteryl esters that have been examined show one or more crystalline fluid phases and many of them have more than one solid phase. I have not been able to detect a crystalline fluid phase in the ethyl, cetyl, menthyl, linaloyl, and phenyl palmitates.

The soaps are another group of substances which can be obtained in a crystalline fluid phase. It has for some time been known that the alkaline oleates show this condition and I have now examined the potassium salts of the fatty acids mentioned above. Of these salts all except the lactate, formate, acetate, and propionate? can be obtained in a crystalline fluid phase. All these salts were obtained in the crystalline anhydrous condition from alcohol. On placing some of the solid crystals on a slide and adding a drop of water the crystalline fluid condition is seen as the salt dissolves forming a transition layer between the anhydrous crystals and the solution. With regard to the existence of fluid crystals in the propionate I am doubtful. If the condition exists at all it is extremely transient. In the butyrate the layer is very thin and difficult to see owing to the extreme solubility of this salt. With the salts of the higher acids the crystalline fluid condition is more evident the higher the acid. The palmitate and stearate show this condition in spite of the fact that they are insoluble in water at room temperature. Sodium palmitate shows the same condition only on warming with water.

As to the action of water in producing this condition it is conceivable that the addition of water produces hydrolysis and that the fluid crystals consist of a mixture of potassium hydrate and fatty acid thus corresponding to the cholesterol-fatty acid mixtures mentioned below. Against this, however, is the fact that these salts are soluble in water, and hydrolysis in solution only occurs in considerable dilution. It seems more probable that the crystalline fluid condition is a hydrate of the salt, the water existing as water of crystallisation.

It appears that the potassium salts of any of the fatty acids

can be obtained in a crystalline fluid condition provided that the corresponding acid has an oily nature.

ANISOTROPIC GLOBULES.

If a mixture of cholesterol and a fatty acid is melted on a slide and the preparation allowed to cool, the cholesterol separates out in the crystalline condition and, in advance of the growing crystals, clouds of anisotropic globules appear which subsequently in most cases solidify, merging in the general mass of crystallisation. Sometimes the globules retain their condition among the solid crystals and reappear on warming. On solidification that part of the preparation in which the globules appear always shows smaller crystals than other parts.

All the fatty acids tried give these globules except lactic, formic, acetic, propionic, butyric? isovaleric? and caproic? but I have not tried the last three fully.

Better results can be obtained if this experiment is carried out quantitatively. If we mix the cholesterol and the fatty acid in equimolecular proportions and melt the mixture we find that, on rapid cooling, the anisotropic globules appear simultaneously over the whole preparation. Later on these globules coalesce to form fluid crystals which are often arranged in interlacing strands forming an open network, the appearance being very similar to that seen in ammonium oleate and other soaps. These fluid crystals are often very persistent lasting at room temperature for some hours. Solidification eventually takes place in the form of bundles of minute needles which bear a striking resemblance to the crystals met with in tumours, adrenals, etc. These crystals are apparently crystals of a mixture or a loose combination of cholesterol and the fatty acid since on heating they are dissociated, the fatty acid melting and the cholesterol crystals floating in the melted acid. The temperature at which the globules appear is often somewhat below the melting point of the fatty acid but varies with the proportion of the two constituents. In some cases the addition of a drop of water facilitates the appearance of the globules and fluid crystals.

For example, if cholesterol and palmitic acid in equimolecular proportions be melted together on a slide and the preparation be cooled moderately rapidly the globules appear at about 58° . The globules then run together and form strands of fluid crystals which eventually solidify in the form of minute wavy needles. If we now heat the preparation the crystals partially melt at about 58° and small crystals of cholesterol are seen floating in the melted acid. These latter crystals do not melt at any temperature obtainable on the stage (79°), and the preparation must be heated above this temperature before the globules and fluid crystals can be again obtained on cooling. If the preparation is from the first cooled very slowly the globules are apt to fail the cholesterol crystallising out in the solid form. Thus this mixture differs entirely in its properties from cholesteryl palmitate. Similar results can be obtained with other acids.

I have not fully investigated proportions other than the equimolecular. This appears to be the most favourable proportion, but proportions of one molecule of cholesterol to two or three of the acid also show very well in some cases.

In the case of the lower fatty acids all the first six acids of the acetic acid series have a remarkable solvent action on cholesterol. If a solution of cholesterol in one of these acids be allowed to evaporate at room temperature, crystals are obtained which contain both constituents but which are not the esters. If the cholesterol-acid mixture is heated the ester is formed, particularly in the case of formic acid. Thus a solution of cholesterol in propionic acid crystallises in long crystals which can be obtained free from any residual acid but this substance differs entirely in its characters from cholesteryl propionate. If these crystals are heated they are dissociated, propionic acid being set free. They are also readily decomposed by a solution of Sodium carbonate. The propionate, however, is a very stable compound and heat and boiling sodium carbonate solution have no effect on it.

We find, then, that cholesterol has the remarkable character of being able to take up fatty acids to form loose combinations which are not the esters. Presumably in these combinations

the acids exist as "acids of crystallisation." This subject is being further investigated by Dr. Craven Moore.

I have not been able to obtain these anisotropic globules on mixing cholesterol with the triglycerides. I once found them with tripalmitin but after many attempts I have been unable to repeat this observation and I conclude that in this case some contamination had taken place.

Apart from the fatty acids, mixtures of cholesterol with cetyl alcohol or glycerine give precisely similar results. Presumably in this case also we have the cholesterol crystallising with "alcohols of crystallisation." In this case we have two substances neither of which shows a crystalline fluid phase, and between which no compound of the nature of an ester can be formed under the conditions of experiment, yet, when mixed together and melted the resulting substance shows on cooling anisotropic globules and fluid crystals.

Mixtures of cholesterol with mono-and di-palmitin behave in a similar way.

Mixtures of cholesterol with the following substances gave negative results:—phenol, thymol, menthol, azobenzene, azoxybenzene, naphthol, naphthalene, naphthylamine, diphenylamine, paraffins and benzene hydrocarbons, toluidin, aniline, volatile oils, etc., etc.

As to the composition of the globules and fluid crystals the question arises whether they are composed of one of the constituents of the mixture separating out from the other or whether each globule and crystal is composed of a mixture of the two constituents. The latter seems to me the more probable view. Cholesterol has no difficulty in crystallising out as such from an excess of fatty acid or alcohol-glycerine and it is only on certain conditions that the fluid crystals appear. The fact that the only substances with which cholesterol gives these globules and fluid crystals are fatty acids or alcohols and that the experiment fails when we use as substitutes for these substances of similar physical characters such as paraffins, essential oils, or triglycerides goes to show that there is some kind of union between the constituents of the mixture in which the anisotropic globules and fluid crystals appear.

If we substitute cetyl alcohol for cholesterol in these experiments we do not obtain any anisotropic globules or fluid crystals but, in the case of the fatty acids the mixture appears to crystallise differently from the corresponding ester. Equimolecular mixtures of cetyl alcohol and palmitic acid, for instance, appear to crystallise as a single substance but differently to the cetyl palmitate.

MYELIN FORMS.

Brücke (1879) and Brockbank (1893) showed that when a crystal of cholesterol is placed in a solution of soap it becomes surrounded by a fringe of cylindrical processes (myelin forms) which appear to sprout out from the crystal and which assume various bizarre shapes. The crystal ultimately disappears the myelin forms floating free in the soap solution. Many of these free forms assume the globular shape; some appear to consist of a capsule containing a more fluid content while the greater number are homogeneous or laminated. If they are examined with polarised light with crossed Nicols, some are seen to be anisotropic, appearing as typical anisotropic globules, while others are isotropic.

These myelin forms are not peculiar to cholesterol. Cetyl alcohol also acts well in soap solution and one of the higher fatty acids may be substituted for either of these and a hydrolysed solution of a potassium salt of a fatty acid, *e.g.*, potassium oleate, shows numerous free myelin forms. The pure soaps, free from fatty acid, do not appear to give myelin forms with water. The most beautiful and varied forms are seen if a drop of ammonia and a drop of oleic acid are allowed to come in contact between a slide and cover glass. Also commercial lecithin, which contains cholesterol, gives myelin forms with water, the lecithin ultimately forming an emulsion or a colloid solution in the water. Lecithin purified by repeated precipitation with acetone does not appear to give myelin forms with water. Cholesterol bromide, cholesteryl palmitate, and cetyl palmitate gave negative results with solutions of the potassium salts.

If a 0.5 per cent. solution of potassium oleate in absolute alcohol be taken and diluted with water from a burette, the

solution being tested with cholesterol from time to time, it will be found that the myelin forms do not appear until the solution begins to react alkaline to phenolphthalein showing that hydrolysis has commenced. This occurs when the strength of the solution is reduced to about 20 per cent. alcohol. If a watery solution be used, myelin forms occur with the clear solution even if this is made alkaline with caustic potash. They are, however, much more marked if the solution be diluted until hydrolysis commences.

I have endeavoured to stain the myelin forms so as to obtain an idea as to their composition but it is difficult to obtain a satisfactory staining. If the potassium oleate solution be coloured with a basic dye such as fuchsine, any free oleic acid will be coloured an intense red owing to the formation of a colour soap. In this case the cholesterol crystals are seen to be surrounded closely by numerous minute, intensely coloured globules of oleic acid combined with the dye. Again if some cetyl alcohol be coloured red by dissolving in the molten alcohol the base of night blue (prepared by precipitating the watery solution of night blue by caustic potash) and allowed to solidify and a portion be introduced into soap solution, some of the resulting myelin forms will be found to be stained a bright blue showing that they contain free fatty acid which has dissolved some of the cetyl alcohol.

It is not necessary to use soap for the production of the myelin forms. They can be obtained if, instead of a soap solution, an emulsion of oleic acid (prepared with the aid of saponin) be used, and a similar emulsion of palmitic acid is also successful on warming. Also cholesterol contaminated with fatty acid or lecithin gives myelin forms with water.

In order to gain a further insight into this phenomenon I have examined the action of the potassium salts of the before-mentioned fatty acids on cholesterol. All these gave myelin form except the lactate, formate, acetate, propionate, butyrate, isovalerate, and caproate.

Thus the appearance of myelin forms obtained by cholesterol and a soap solution appears to be conditioned by the insolubility of the corresponding fatty acid in water.

If we examine the myelin forms and free globules we find that they have not all the same characteristics. Some of them are isotropic, others anisotropic. Of the anisotropic forms some can be seen to be composed of minute fluid crystals arranged with their axes at right angles to the free surface while others show no apparent crystalline structure but appear to be composed of layers arranged parallel to the free surface. The crystalline forms exhibit the highest degree of anisotropism and often lose this character on heating, regaining on cooling. They often show iridescent colours. In the stratified forms, on the other hand the anisotropism tends to increase on heating and is not lost at any temperature obtainable on the stage. In this they resemble starch granules which are anisotropic but not crystalline. These forms pass insensibly into the isotropic forms some of which become anisotropic on heating.

The same is true of the globules seen in the tissues. These vary in the intensity of their anisotropism and in the majority this character is lost on heating, while in others it is rather intensified. If the brightest globules are heated until they become isotropic and examined on cooling minute spindle-shaped fluid crystals are seen to appear in them which by coalescing give the typical anisotropic globule.

The appearance of a black cross on the anisotropic globule and the corresponding markings on the cylindrical forms appears to be due to one of two conditions:—either the globules and cylindrical forms are composed of crystals arranged with their axes at right angles to the free surface; or they are composed of laminae arranged parallel to the free surface.

It seems to me that the introduction of a selenite will help in differentiating these forms, the distribution of colours being different in the two cases, but I have not investigated this point fully.

Myelin forms can also be obtained if pure cholesterol crystals are heated to 130° — 140° in glycerine, the crystals becoming surrounded by a fringe of anisotropic cylindrical processes which mostly solidify on cooling. Very good forms are produced by making an emulsion of cholesterol and glycerine at a temperature just above the melting point of chole-

terol. After cooling, each drop of cholesterol is seen to be surrounded by perfect myelin forms and numerous anisotropic globules float free in the glycerine. Most of these are solid while some remain fluid for a long time at room temperature. Myelin forms can also be obtained if cholesterol be heated on the warm stage with a mixture of alcohol and glycerine.

If cholesterol be warmed with concentrated phosphoric acid myelin forms and anisotropic globules are produced apparently budding out from the crystals.

The explanation of the myelin forms in the case of cholesterol and soap solution appears to be that the cholesterol introduced into, *e.g.*, potassium oleate solution determines the deposition on it of a film of oleic acid in which it partially dissolves and with which it, perhaps, combines, and that it is this film which gives rise to the myelin forms probably by variations in surface tension. The whole process of myelin formation is, in fact, identical with the process of the formation of a spontaneous emulsion. The myelin forms produced with cholesterol and glycerine are probably associated with the cholesterol-glycerine mixture which gives the anisotropic globules. The explanation of the myelin forms given with phosphoric acid is not so clear. Possibly we have to do with another cholesterol-acid mixture but, owing to the different behaviour, the globules appearing on warming rather than on cooling, it is probable that we have to do with a phosphoric acid ester.

We see then that there is a close correspondence between anisotropic globules and myelin forms. When a mixture of cholesterol and a fatty acid shows anisotropic globules, then cholesterol introduced into a solution of the corresponding potassium salt shows myelin forms. Also if a drop of water be added to a mixture which shows the globules and fluid crystals myelin forms shoot out into the water and, at the same time, water penetrates into the mixture. Again, myelin forms, which become free, often assume the globular shape and then appear as anisotropic globules; and also in a mixture of cholesterol with a fatty acid or cetyl alcohol which shows the globules cylindrical and branched forms are often seen exactly resembling myelin forms. In fact, if a cholesterol-fatty acid mixture be carefully

watched as it cools, the first structures to appear are often extremely long, fine, hair-like threads, often in vigorous movement, and the globules result from these by the sudden contraction of the long threads. These appearances exactly correspond with appearances described in certain cerebro-spinal fluids by Dr. F. C. Eve at the meeting of the British Medical Association in 1907.

SUMMARY OF THE FACTS OBSERVED DURING THIS INVESTIGATION.

1. The crystalline fluid phase of the cholesteryl esters is in some a stable condition at definite temperatures and in others it exists only as a metastable condition at temperatures below that of the melting point of the solid crystals.

2. The potassium salts of all the fatty acids examined except the lactate, formate, acetate, and propionate can be obtained in a crystalline fluid phase at room temperature.

3. Cholesterol gives myelin forms with watery solutions of all the potassium salts mentioned except the lactate, formate, acetate, propionate, butyrate, isovalerate, and caproate.

4. Cetyl alcohol and the higher fatty acids also give myelin forms with solutions of the potassium salts of the higher acids.

5. The myelin forms in these cases are associated with the deposition of fatty acid from the solution on the cholesterol or cetyl alcohol. The fatty acid thus deposited dissolves some of the cholesterol, etc.

6. Cholesterol mixed with a fatty acid—best in equimolecular proportions—forms a mixture, or rather an unstable combination, which behaves quite differently to the corresponding ester.

7. In the case of the higher acids these unstable combinations show anisotropic globules and fluid crystals and give myelin forms with water. The combination is broken up on heating and forms again on cooling. With the lower acids the combinations can be obtained in a solid crystalline condition and are broken up on heating.

8. Cholesterol mixed with cetyl alcohol, glycerine, or mono- or di-palmitin forms unstable combinations which show anisotropic globules and fluid crystals and give myelin forms with water.

9. Cholesterol also gives myelin forms and anisotropic globules when warmed with concentrated phosphoric acid.

10. Cholesteryl esters, when pure, do not give myelin forms with water nor do they show definite anisotropic globules. If, however, they contain an excess of either constituent they give globules and myelin forms readily.

11. The cholesterol-fatty acid combinations, owing to the formation of myelin forms, can become intimately mixed with water with the eventual formation of an emulsion. This is not the case with the esters which are extremely stable compounds.

12. The crystals and globules in the tissues, in some cases, can be shown to contain cholesterol and a fatty acid which becomes separated on warming. In other cases the globules show no evidence of fatty acid.

13. Anisotropic globules are not necessarily of a crystalline structure. Some are definitely composed of minute fluid crystals arranged radially and these show the highest degree of anisotropism. Such globules often become isotropic on heating regaining their anisotropic characters on cooling. In other globules the anisotropism resembles that of starch and tends to increase on warming. No definite line can be drawn between such globules and similar globules which are isotropic.

14. The same may be said *mutatis mutandis* of the myelin forms. In the crystalline form the crystals are arranged with their axes at right angles to the free surface whatever shape the form may take.

CONCLUSIONS DEDUCED FROM THE FOREGOING FACTS.

If we collect these observations and attempt to deduce conclusions from them we arrive at the following results:—

1. The potassium salts of those fatty acids which are of an oily nature can be obtained in a crystalline fluid condition. This condition probably represents a hydrate of the salt.

2. Cholesterol and some other substances such as cetyl alcohol, or one of the higher fatty acids, give myelin forms with the watery solutions of the potassium salts of those acids which are of an oily nature and which are insoluble in water.

3. These myelin forms are due to variations in surface tension acting on the film of cholesterol—fatty acid mixture formed by the deposition of fatty acid from the solution on the cholesterol.

4. Cholesterol has the peculiar property of combining with fatty acids to form crystalline compounds which are quite different from the esters. In these combinations the acids presumably exist as “acids of crystallisation.”

5. Cholesterol forms with alcohols similar crystalline combinations in which the alcohols exist as “alcohols of crystallisation.”

6. Anisotropic globules occurring in the tissues are no evidence of the presence of oleates or of cholesteryl esters. More probably they consist of a cholesterol-fatty acid or similar mixture.

7. Anisotropic globules and anisotropic myelin forms are closely related and appear to be identical structures under varying conditions differing only in their shape.

8. The formation of these unstable combinations of cholesterol with fatty acids and other substances suggests that cholesterol may play an important part in fat absorption and fat metabolism and in other physiological and pathological processes.

9. It is probable that many structures which have been described as cell inclusions, parasites of different sorts, hæmiconia, etc., find their explanation in myelin forms and such structures should always be examined with reference to this point. Myelin forms assume an endless variety of shapes and often show most vigorous movements closely simulating the movements of living organisms.

10. The view that cholesteryl esters can absorb large quantities of water appears to be erroneous. This property is characteristic rather of the cholesterol-fatty acid combinations.

It will be seen from these conclusions that I differ in many respects from others who have studied these anisotropic globules. Practically all who have studied the question have come to the conclusion that these globules are composed of protagon, oleates or cholesteryl esters. The evidence that these authors bring

forward as to the existence of esters is very imperfect and in many cases it seems to depend on the fact that they detect the presence of cholesterol and a fatty acid, which they would equally find if the globules consisted of the peculiar mixtures which I have described. When cholesterol and fatty acids exist together in solution it is very difficult to separate them by simple crystallisation, and those who have worked at the subject have separated the constituents by means of caustic potash or sodium ethylate. Some help might be gained by saponification with sodium carbonate which has no effect on the esters while it readily breaks up the more unstable combination.

I must criticise the paper of Adami and Aschoff more fully.

In the first place these authors appear to use the presence of anisotropic globules as a test of the crystalline fluid character of a substance. A substance may, however, show fluid crystals and not anisotropic globules and *vice versa*.

In the next place they state that potassium palmitate and stearate do not show anisotropic globules under any conditions. I find, however, that these salts, like the other potassium salts, assume the crystalline fluid phase at room temperature on the addition of water to the anhydrous crystals and, if they are at all contaminated by some free fatty acid, they exhibit myelin forms and anisotropic globules with water.

Again these authors prepared their cholesteryl esters by heating together cholesterol and a fatty acid. In this method of preparation it is very difficult to obtain the ester in a pure condition and it is probable that the substances they worked with were contaminated with the more unstable compound. Thus I find that cholesteryl palmitate when pure will not give anisotropic globules even if it is made into an emulsion with glycerine or water. If, however, the ester contains a slight excess either of cholesterol or of palmitic acid, it gives myelin forms and globules readily. On the other hand an equimolecular mixture of cholesterol and palmitic acid when melted and allowed to cool exhibits a magnificent display of anisotropic globules and, from the description of their methods it is evident that Adami and Aschoff were working with such a mixture.

Cholesteryl esters are not formed by heating together cholesterol and a fatty acid in the presence of water.

Adami and Aschoff conclude that fatty acid is to be considered an essential constituent of myelin. My observations on equimolecular mixtures of cholesterol with cetyl alcohol or glycerine show that this statement may have to be reconsidered, and it is possible that some of the globules may be composed of a mixture of cholesterol with some substance which is not a fatty acid.

With regard to choline oleate I have no experience, but there does not seem to be any evidence that such a compound exists in the body.

Adami and Aschoff state that cholesteryl oleate is in a crystalline fluid condition at room temperature. I find, however, that it undergoes complete solidification in 12—18 hours.

I may refer readers to the article by Dr. F. Craven Moore in the present volume. He has been working at the subject from the chemical aspect while I have been studying it from the point of view of the histologist, and it is interesting to note that from these different aspects we have arrived at the same conclusion as to the existence of these cholesterol-fatty acid combinations which are distinct from the esters.

I have to thank Dr. J. F. Thorpe for advice on some of the chemical aspects of this investigation.

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GAS-CONTAINING CYSTS OR AIR-BLADDER TUMOURS.

By W. MAIR,
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(From the Pathological Laboratory of the University of
Manchester.)

IN Andral's 'Treatise on Pathological Anatomy,' in the chapter on Diseases of the Alimentary Canal, we find under the heading "Exhalation of Gases," the following statement. "One of the frequent effects of putrefaction is the formation of gases in the substance of the gastro-intestinal parietes. When bodies are opened in summer ever so soon after four and twenty hours after death, the mucous membrane of the stomach and intestines is found puffed up in many places by gases accumulated in the subjacent cellular tissue. This emphysema is not, however, in all cases the result of cadaveric decomposition, but sometimes takes place during life. The case recorded by M. Jules Cloquet is of this description. A scrofulous patient, twenty years of age, died at the *Hôpital St. Louis* in the last degree of marasmus, in consequence of a caries of the vertebral column. The body was opened shortly after death, before it had begun to show the least sign of putrefaction. There was considerable emphysema of the cellular tissue that unites the different coats of the stomach, so that its parietes appeared to have been inflated, and in several places were near an inch in thickness. The mucous membrane, which was embossed, was pale and free from any appreciable lesion. The two anterior folds of the great omentum, which are attached to the greater curvature of the stomach, were also separated from each other by gas, and the same was the case with the small omentum. There had been no symptom denoting any affection of the stomach, except a complete anorexia for several days before death. Similar gaseous exhalations have been seen in other portions of the submucous cellular tissue, especially in the substance of the parietes of the gall bladder. In laying before the faculty the case just cited, M. Cloquet stated that he had often observed

the same kind of emphysema in pigs recently slaughtered. In one of these, he found another very remarkable kind of emphysema: to the intestines and mesentery were attached in clusters large bundles of membranous vesicles, which were roundish, transparent, and *filled with air*; they were each appended by a narrow thin vascular stalk. Their size varied from that of a pea to that of a small nut."

I have quoted the above passage in full because it appears to me to draw a very clear distinction between the emphysema which occurs as a result of bacterial action either post-mortem or immediately before death, and a quite different condition, namely, the occurrence of gas-containing cysts described above as "another very remarkable kind of emphysema." In another place Andral refers to the secretion of gases from the blood in the air-bladder of fishes, and it is evident that he regards the gas in these cysts as being of similar origin.

The condition appears to be not uncommon in the pig. Mr. Shattock has kindly called my attention to the fact that there are two examples of it in the Museum of the Royal College of Surgeons (Nos. 293 and 294, Hunterian specimens). One of them (No. 293) is thus described. "A portion of the rectum of a Hog, of which the peritoneal coat is in many places, and especially by the sides of the meso-rectum, covered by groups of thin-walled, transparent, membranous cysts, attached by pedicles, or having broader bases, and containing air." The same specimen is engraved in Hunter's Works where it is described as follows: "A portion of intestine of a hog, the peritoneal coat of which is covered in several places with small pellucid cysts containing air. It was sent to me by my friend Mr. Jenner, surgeon at Berkley, who informed me that this appearance is found very frequently upon the intestines of hogs that are killed in the summer months." Hunter also refers to this specimen in the following passage: "That air is either formed from the blood, or let loose by some action of the vessels, both naturally and from disease, is an undeniable fact. We find air formed in some fishes to answer natural purposes; for in those whose air-bladders do not communicate externally (many of which there

are) we must suppose it to have been formed there. We also find it in animals after death, and I have a piece of the intestine of a hog which has a number of air-bladders in it. Mr. Cavendish was so kind as to examine this air, and he found 'it contained a little fixed air; and the remainder not at all inflammable, and almost completely phlogisticated.'” A specimen with the history of which the names of Jenner, Cavendish, and Hunter are associated is certainly one of no common interest. “Surely never, on an object so mean to common apprehensions, did such rays of intellectual light converge, as on these to which were addressed the frequent and inquiring observations of Jenner, the keen analysis by Cavendish, and the vast comparison and deep reflection of John Hunter. Surely never were the elements of an inductive process combined in such perfection. Jenner to observe; Cavendish to analyse; Hunter to compare and reflect.” Thus eloquently does Sir James Paget express the emotions aroused by a study of the specimens in question. But this is a digression. It will be observed that Hunter, like Andral, regarded these cysts as being quite analogous to the air-bladder of fishes.

Under the name “mesenterial emphysema of hogs,” Ostertag describes bunches of small transparent gas-containing cysts attached to the mesentery close to the bowel, or to the bowel itself. There is a good engraving illustrating the condition. A number of authors are mentioned in connection with it but no references are given. It is stated to be found in the carcasses of pigs which are normal in every other respect, and to be well known to experienced meat inspectors as a frequent and striking phenomenon.

In man the occurrence of gas-containing cysts within the abdomen is rare. I have only found references to six cases. In four of these the cysts occurred in the wall of some part of the intestine; in the other two they were found in the wall of the urinary bladder. In the vaginal wall the condition is commoner. In 1888, Eisenlohr collected thirty-five cases from the literature of the subject. Although of little pathological importance, these gas-containing cysts are, as Ostertag says, a striking phenomenon, and have given rise to much discussion

and much ingenious speculation as to their nature and mode of origin.

I have myself had an opportunity of examining two cases. In both of these the gas-containing cysts were removed from the abdomen by surgical operation during life. For the first case I am indebted to Mr. A. B. Mitchell of Belfast. While doing a gastro-enterostomy on a young man who suffered from pyloric obstruction, Mr. Mitchell found the tumour by accident and resected the piece of small intestine involved. The patient made a good recovery in spite of the double operation. The tumour had apparently given rise to no symptoms. Plate I. represents a photograph of the specimen, one-third of the natural size. For the use of this photograph I wish also to express my thanks to Mr. Mitchell.

The specimen comes from about the middle part of the small intestine, about nine inches of the gut having been removed. Of this six inches are involved in the tumour which consists of a lobulated mass of gas-containing cysts surrounding the gut. The individual cysts are very numerous and vary in size from that of a large walnut downwards, the smallest being just visible to the naked eye. The great mass of the tumour is situated at the side of the bowel opposite its mesenteric attachment. With the exception of a few very small cysts close to the gut the mesentery itself is not involved. On the peritoneal aspect the cyst walls are very thin and quite transparent. As already mentioned the mass is lobulated so that the bunches of cysts can be separated from one another to some extent. The cysts are connected together by strands of tissue which from its colour is evidently vascular. A small amount of fluid can be seen in some of the cysts, but the striking feature of the specimen is that the cysts contain gas under sufficient pressure to keep their walls tense. One or two of the larger cysts project slightly into the lumen of the bowel opposite the mesenteric attachment; here the wall is not transparent but is formed of mucous membrane. The cysts do not communicate with one another. When one is punctured it, and it alone, collapses with the escape of an odourless gas. As it was thought possible that the condition might be due to

bacterial action cultures were made from the interior of some of the cysts on nutrient agar. The tubes after incubation remained sterile.

Before giving the results of the microscopical examination it will be convenient to refer to the second case which I have examined. The specimen in question has been preserved in the collection of the Pathological Laboratory of the University of Manchester. The case has already been published by Mr. Thorburn, and with his permission I have re-examined the histological structure of the tumour. The patient was a woman with pyloric obstruction due to a cicatricial band of fibrous tissue. Full details of the clinical history and operation are given in Mr. Thorburn's paper from which I quote the following description: "During the removal of this band there was now found to the right of the great omentum a collection of rounded cystic masses, extending into the right hypochondrium. The numerous cysts varied in size from that of a small pea to that of a walnut, and were closely packed together in the form of a cone, of which the apex lay some two inches from the middle line, while the base rested near the hepatic flexure of the colon and deeply in the right flank. With much trouble the entire mass was dissected away from the omentum and from the peritoneum of the stomach and transverse colon, to which it was also attached. It then closely resembled a cluster of hydatids, arranged in a cone, with a base about three inches in diameter and having a vertical measurement of some five inches. Each little cyst had a thin transparent but well-defined wall; they were separated only by a delicate fibrous tissue of greater tenuity than the omentum itself. Some of the cysts contained a thin, almost colourless fluid, rather more glutinous than serum, but the majority were filled with an inodorous gas. There was no trace of suppuration anywhere. The excision of this remarkable cone of cysts was followed by the discovery of an almost precisely similar collection upon the left side of the omentum, with its base passing beneath the spleen." This second tumour was not excised.

In this as in the other case the gas-containing cystic masses had nothing to do with the patient's symptoms and were merely

an accidental discovery. In neither of the cases, unfortunately, was an immediate collection of the gas made for purposes of analysis.

The microscopical examination was carried out similarly in the two cases. After formalin fixation pieces were cut from the tumours, embedded in paraffin, cut in serial sections, and stained in various ways. During the process of embedding it was necessary, in order to secure proper penetration, to puncture as many of the small cysts as possible and gently express the gas.

The histological structure of the tumour in the two cases is almost identical. The smaller cysts are lined by a layer of finely granular protoplasm with nuclei arranged in a single row or irregularly scattered several rows deep (Fig. 3). There is no definite demarcation into separate cells. The thickness of the layer and the number and arrangement of the nuclei vary considerably. Thus we find at places a definite epithelial lining, consisting of a single layer of cells resting directly upon the fibrous stroma with no basement membrane interposed. Even here there is no distinct separation between the different cells. In other places irregular multinucleated masses of protoplasm project into the interior of the cyst. Mitotic figures are fairly frequent in these lining cells and the multinucleated cells often show vacuolation (Fig. 6). Occasionally the cells are found lying free in the interior of the cyst. The walls of the larger cysts are, in places at least, of extreme thinness, consisting, as seen in section, of one or two fibrils with a few nuclei or nucleated spindle cells either on the surface or between the fibrils. At such places the cyst can hardly be said to have a definite epithelial lining. Where the wall is slightly thicker capillary blood-vessels appear in it, and indeed the vascular arrangement in the cyst wall is one of the most striking features in the structure of the tumour. At places there is a great development of thin-walled and wide tortuous vessels in the septa between the cysts, the blood being separated from the interior of the cyst only by the thin walls of the vessel itself and by that of the cyst (Fig. 1). By means of serial sections I have been able to satisfy myself that all these variations in the struc-

ture of the cyst wall can be found in one and the same cyst. The supporting framework of the tumour consists of connective tissue in which as a rule blood-vessels are well developed. At places the tissue is condensed in the form of distinct nodules (Fig. 2), with well developed fibrils, inconspicuous nuclei, and no blood-vessels. In some of these nodules active proliferation of cells resembling fibrocytes is to be seen and the tissue elements have become separated from one another leaving clear spaces (Fig. 4). A very characteristic appearance in the stroma is the presence of enormous multinucleated cells. These cells often occur in the nodules already mentioned and are sometimes surrounded by clear spaces or by proliferating fibrocytes (Fig. 4). They often show vacuolation and the nuclei resemble those found in the lining of the cysts. Some of these giant cells measure as much as 250μ in diameter, and nuclei to the number of several hundreds can be counted in a single section (Fig. 5). There can be little doubt that the proliferating "fibrocytes" and giant cells play an important part in the development of the cysts. That the vacuolation of these multinucleated cells is not due to the presence of fat is shown by osmic acid preparations. In Mr. Thorburn's case I have not found the definite fibrous nodules; the stroma generally is of a looser texture resembling oedematous fibrous tissue, and the development of blood-vessels in the septa is not quite so well marked. In Mr. Mitchell's case the giant cells are not so large and are more regular, usually round in shape. With these reservations the above description applies equally to both tumours.

The definite structure of this tumour appears to me to render it very improbable that it is of inflammatory or infective origin. With the exception of the proliferation of fibrocytes and the presence of giant cells there is nothing in the histological appearances to suggest an inflammatory process and these appearances can equally well be explained on other grounds. There is no exudation or emigration of leucocytes nor any accumulation of round cells. The dilated blood-vessels do not show any increase in the number of leucocytes, and their appearance is not due to an inflammatory dilatation of previously existing vessels but to a new formation of vessels of a special

type. I have examined sections specially stained in various ways and have been unable to detect the presence of bacteria or other parasites. I believe that the tumour is a true neoplasm, the cells of which have the power of secreting gas, and that its development takes place somewhat as follows. The youngest stage is the fibrous nodule (Fig. 2). In this there occurs a proliferation of cells which are indistinguishable histologically from fibrocytes (Fig. 4), but are undoubtedly endowed with very different physiological characters. By division of the nuclei without cell division the large multinucleated masses of protoplasm are formed. In these gas bubbles appear and gas accumulates around them under sufficient pressure to distend the tissues (Fig. 5). Concurrently with the gas-cyst formation proliferation of other cells gives rise to the formation of blood-vessels with the structure and arrangement described above. As the gas accumulates the cyst walls become thinned and the giant cell or cells, flattened out on the interior of the cyst wall, give rise to the incomplete epithelial lining. The thin-walled blood-vessels in the septa between the cysts are obviously for the purpose of securing a secretion of gas from the blood.

The secretion of gas by cells is not unknown in the animal economy. The work of Haldane and Lorrain Smith has shown that the cells of the lungs alveoli take an active part in the exchange of gases. In the air bladder of fishes, which this tumour resembles more than any other normal structure, gases are secreted from the blood. The vascular arrangements especially, in this tumour, resemble those in the air-bladder of fishes.

For a proper understanding of the nature of these tumours it is obviously important to have an accurate knowledge of the composition of the gas contained in them. Unfortunately in this respect our knowledge is not yet very complete. Several analyses have been made by different observers in the case of cysts from pigs and from the human vagina. The modern writers agree that they contain oxygen and nitrogen with very little carbon dioxide. It will be remembered that Cavendish, in his report to Hunter, found a little carbonic acid and for the rest nitrogen. The percentage of oxygen is variously stated at

from 16 to 20 %. In the case of cysts from the human intestine no quantitative analyses have been made. All that we know about the gas in these cases is that it is odourless and not combustible. The close correspondence of some of the analyses with the composition of atmospheric air makes it questionable if the authors realised the rapidity with which diffusion of gases can take place through such a thin membrane as that composing the cyst walls. There is usually no statement as to the time at which the analysis was made, and it is quite possible that admixture with atmospheric air may have taken place. An accurate analysis of the gas from a sample obtained at the earliest possible moment after removal of the tumour is therefore much to be desired. Obviously the most suitable material for this purpose would be that obtained by surgical operation or, in the case of pigs, at the abattoir. It may be mentioned here that the gas in the air-bladder of fishes consists chiefly of oxygen and nitrogen, the oxygen being present in considerably greater proportion than in atmospheric air. In the case of fishes from great depths especially, the oxygen often amounts to 80% of the whole, and it must here be secreted against enormous pressure. Bohr has shown there occurs in the air-bladder "a true secretion of a highly oxygenated gas mixture which is so far under nervous control that it fails when the branches of the vagus which supply the air-bladder are cut."

As the view that these gas-containing cysts are true neoplasms, analogous in structure and function to the air-bladder of fishes, is here put forward, so far as I know, for the first time, I must now refer to the literature of the subject, and adduce additional arguments in support of this view, while criticising some of those previously entertained.

The first case of gas-containing cysts of the intestine with a description of the microscopical appearances was published in 1876 by Bang of Copenhagen. I have not seen the original paper, but it is fully quoted by Winands. The condition was found in a woman who died from intestinal obstruction due to volvulus. The wall of the intestine towards the lower end of the ileum was affected for a length of two feet. Cysts varying in size from that of a pea to that of a bean were present in

large numbers in the coats of the intestine. The peritoneal coat was thickened by a new growth which in small part showed a compact structure but was mostly in the form of thin sheets and strands. The whole of this structure contained an immense number of cysts, the smallest being barely visible to the naked eye while the largest were the size of a pea. All the cysts contained gas and no fluid. Microscopically the cysts in the wall of the intestine were found to lie mostly between the muscle fibres from which they were separated by a layer of fibrillar tissue. Some were situated in the submucosa. The inner surface of the cysts was lined with an endothelium of which most of the cells were very large and multi-nucleated. The cysts in the new growth of the peritoneum had very thin walls of connective tissue with a lining endothelium exactly like those in the wall of the intestine. For the rest, this new growth consisted of a fibrillar connective tissue with a large number of cells of which some were round and small, others oval and larger, and others spindle-shaped and of very considerable size. The tissue was very vascular and some of the vessels were dilated. Dilated lymph channels containing large cells and a net-work of fibrin were also seen. These did not communicate with the cysts. Bang considers that the cysts may have arisen in two possible ways, either by dilatation of pre-existing lymphatic spaces, or secondly, as a true neoplasm. As he found no connection between the lymph spaces and the cysts he thinks that the first suggestion must be rejected. He thus comes near to what I believe to be the true explanation of the condition. The cyst formation begins, according to Bang, with the enlargement of a connective tissue cell to form a giant cell. The tissue space around this cell then becomes filled and distended with *serous fluid*, probably as a result of the vital activity of the cell. The production of gas in the cysts is regarded as a secondary change. As Eisenlohr has pointed out there is absolutely no analogy to be found for this change of serous fluid into gas and no suggestion whatever is given by Bang as to why or how it takes place. He had apparently no microscopical evidence of fluid even in the smallest cysts. One notices here a reluctance to admit the possibility of the secretion

of gas by the body cells, an idea which presented no difficulties to the earlier writers like Hunter and Andral. In the later literature of the subject the possibility of such a secretion never seems even to have been considered.

As much of the discussion on the aetiology of these gas-containing cysts has arisen in connection with their occurrence in the vagina, it will be convenient here to give a short resumé of what is known as to this condition. It has been described by many writers under various names (*Colpohyperplasia cystica*, *Emphysema vaginae*, etc.). It occurs most frequently, though by no means exclusively, in pregnant women, especially towards the end of pregnancy. The cysts occur in large numbers in the mucous membrane or submucosa and contain gas which escapes with an audible hiss when they are punctured. Occasionally cysts containing fluid occur along with the gas cysts. In one of Schmolling's cases the cysts were observed to contain at first gas, and later serous fluid. The condition usually disappears shortly after parturition.

A bibliography is given by Breisky who regards the condition as not very uncommon. He had himself seen twenty examples of it. Very good coloured engravings of the appearances as seen with the speculum are to be found in a paper by Chénevière. The microscopical appearances have been most fully described by Chiari. In two cases which came under his own observation he found giant cells in the tissue spaces and lining the smaller cysts. The close connection of the cysts with dilated blood vessels was also noted. Chiari also investigated microscopically five specimens of the condition in the Prague museum, and in three of these he found quite similar appearances. He pointed out the striking resemblance of the histological features to those of Bang's case of "intestinal emphysema." Chiari thinks it not improbable that the gas contained in the cysts is atmospheric air which has found its way through minute lesions in the mucous membrane into the lymphatic spaces. Such an explanation of the origin of the gas cannot be seriously regarded as possible. Indeed much of the speculation as to the aetiology of these vaginal cysts is characterised by a profound ignorance or neglect of elementary

facts of physiology and pathology. As another example of the ingenuity which may be expended in the endeavour to avoid the obvious, I may mention the suggestion of one writer that the gas in the cysts may consist of trimethylamine. If the reader is further interested in the subject he may consult Eisenlohr's paper where there is a full discussion and criticism of all the various theories of this nature.

More worthy of serious consideration is the view, first suggested by Klebs, that these cysts are of infective origin. Klebs found numerous micrococci and bacteria inside the cysts in a specimen in the Prague museum, and Eisenlohr's work, in which the view of the bacterial origin of these cysts is elaborated, was done under Kleb's direction. The material at Eisenlohr's disposal was obtained *post mortem* from two cases. In the first case, that of a woman who died from heart disease, gas-containing cysts were found in the wall of the intestine and also in the vagina. In the second case the cysts were found in the wall of the bladder in a woman who died from cancer of the ovary. The microscopical appearances were the same in both cases and the description corresponds closely with that already given more than once in the present paper. In particular the presence of giant cells and dilated blood-vessels may be mentioned. Eisenlohr also found dilated lymph spaces lined by endothelial and multinucleated cells and he lays great stress on the fact that these communicated with the cysts, and that the neighbouring cysts communicated with one another.

In the lymph spaces and in the cysts Eisenlohr found clumps of bacteria. These were exceedingly small, requiring for their demonstration a magnification of 2500 diameters. Eisenlohr himself admits that with lower powers they might easily be mistaken for albuminous deposits or disintegrating cells, and this I believe to be the true explanation of the appearances which I have also found in my own preparations. In one case only, the bladder case, cultures were made. Here the section took place 24 hours after death. From the mucous membrane of the bladder and from the gas cysts a bacillus was isolated which showed motility, did not liquefy gelatine, and produced

gas in certain media. Its characters are not further described. There is no evidence that this bacillus was the same as those seen in the sections, and there can now-a-days be little doubt that it was in fact *B. Coli* or a related form, and that its occurrence was merely a post mortem phenomenon. We cannot admit, therefore, that Eisenlohr has made out his case for the bacterial origin of these tumours.

Marchiafava has described a case in which serous cysts occurred in the wall of the intestine. This case is of interest here because of the occurrence of multinucleated cells in the tissue spaces and lining the cysts. We have already seen that in some cases cysts containing fluid occur in the vagina along with gas containing cysts.

In the case described by Winands the gas cysts occurred in the wall of the ileum over a length of several feet, and also in that of the large intestine. They were found *post mortem* in the body of a woman who had suffered from chronic gastric ulcer and dilatation of the colon. The lungs showed tuberculosis and a condition of chronic adhesive peritonitis is mentioned. Gas cysts occurred also in the adhesions, and it is not clear whether there was a tuberculous peritonitis, or whether the adhesions mentioned were the result of the cystic new-growth. Higher up in the intestine in this case there was an interesting condition which throws some light on the natural history of these tumours. On the inner aspect of the bowel there were seen pale areas with slightly raised margins suggesting at first sight ulcers. The mucous membrane was, however, continuous over these areas and on further examination they were found to be due to the presence of cysts which had collapsed, fibrous adhesions having taken place between the apposed walls. The microscopical appearances in Winand's case were exactly similar to those previously described. Bacteria were present, but the author regards them as of little importance. He expressly declines to offer an opinion on the aetiology of the condition, but regards Eisenlohr's case for the bacterial origin of the cysts as certainly not proven. Winand attaches much importance to Marchiafava's case referred to above and thinks it probable that in all cases the cysts at first contain fluid.

In Winand's paper reference is made to an inaugural thesis by Camargo (Geneva, 1891), in which gas cysts were found in the wall of the large intestine of a man who died from pulmonary tuberculosis. Camargo also described a case where the condition occurred in the wall of the bladder. He accepted Eisenlohr's explanation of the condition.

Ostertag, describing the condition in pigs, thinks that it must be infective in origin, and from certain histological appearances which he does not further specify, he is of opinion that it is due to a yeast. All his cultures, however, made from quite fresh specimens, yielded negative results.

If we review the facts summarised in the foregoing we see that quite a considerable number of cases of gas-containing cysts have been described in the human subject which agree in all essential respects both as regards their naked-eye and their microscopical appearances. The condition is commonest in the vagina; the site next in order of frequency is the intestine. There can be little doubt that it is the same condition which occurs more frequently on the intestine and in the mesentery of the pig. The explanation of all these cases must be the same. Apart from the view that the condition is a true neoplasm which is capable of secreting gas, the only intelligible explanation which has been suggested is that it is due to infection by bacteria or other parasites. In this case we must suppose that the giant cells are of inflammatory origin, and that the gas is produced by a fermentative process from the body juices. Apart from the fact that such bacteria or parasites have never been satisfactorily demonstrated it appears to me quite impossible to explain the structure of the tumour on these lines. How, in this case, do the cysts come to be separate from one another and to possess in part at least, a definite protoplasmic lining consisting of multinucleated cells? How are the vascular plexuses in the cyst walls to be explained? If, as appears probable, the contained gas consists chiefly of nitrogen and oxygen this fact would also be strongly against the bacterial theory. The explanation of the fact that certain of the cysts contain serous fluid appears to be simple. It is easy to understand how a serous exudate might take place into a gas-containing cavity

with absorption of the gas; this sequence of events has actually been observed in vaginal cysts. It is quite another matter to suppose, as certain authors have done, that a serous exudate can be replaced by or converted into gas. For such a process there is no analogy, and apart from bacterial action it would appear to be quite impossible. When in other tumours we find cystic spaces filled with a definite secretion no difficulty is felt in supposing that the secretion is due to the vital activity of the lining cells; thus in tumours of the liver bile may be secreted, and thyroid tumours even in their metastases secrete colloid substance. Why should not tumour cells secrete gas? It may be said that there is no analogy for this process in the mammal. I have already indicated that an analogy may be found in the activity of the lining epithelium of the lung alveoli. But even if we have to go to the fish for an exact analogy, surely this does not render its occurrence as a pathological process in mammals any less probable. Mammals are certainly descended from a fish-like ancestor

It is admitted that the tumour does not correspond closely in its manner of development to that of the air-bladder of fishes, which is formed as a diverticulum from the alimentary canal, but the final result is a structure which, especially in its vascular arrangements, very closely resembles that of the air-bladder. Of its resemblance in function there can be little doubt. In support of the view that there is a true homology between these tumours and the air-bladder of fishes it may be further pointed out that the sites in which the tumours occur are in close relationship developmentally with the alimentary canal.

The mammalian lung is homologous with the air-bladder of fishes, although it has undergone in the course of evolution, a complete reversal of function as regards the direction of the gaseous interchange. If the view of these gas-containing tumours expressed above be correct we might expect to find similar tumours in connection with the lung. So far as I know no case exactly corresponding to them has been described. Sir Thomas Barlow has described a gas-containing cyst in the lung which was completely cut off from all communication with the air passages. I have myself observed in an adult a small

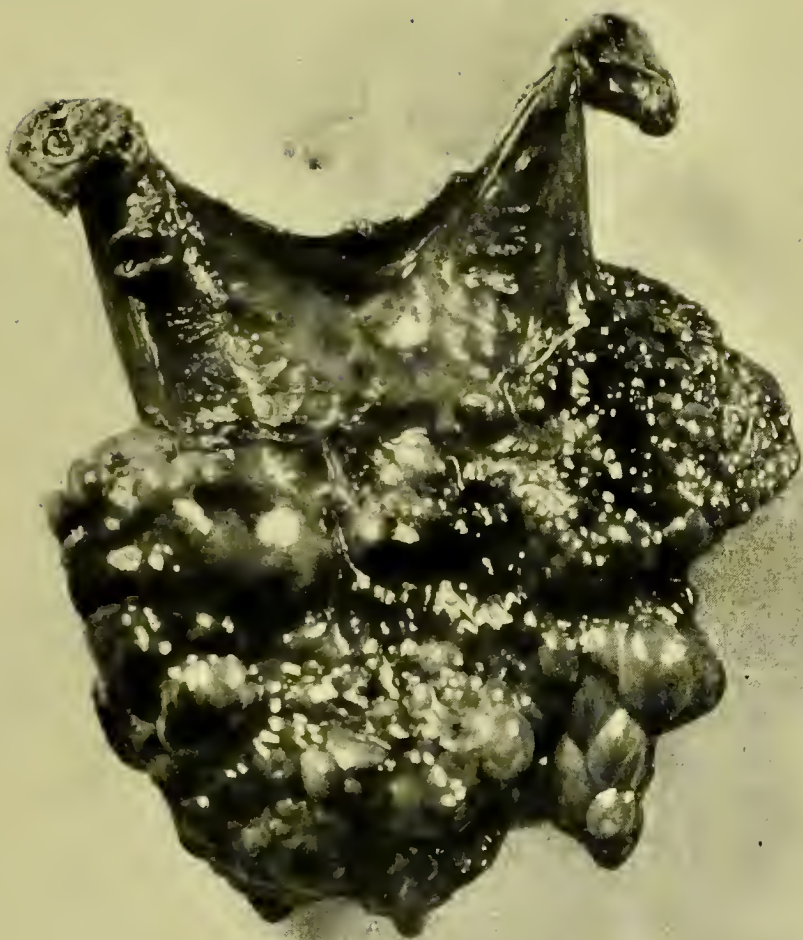


Plate I.

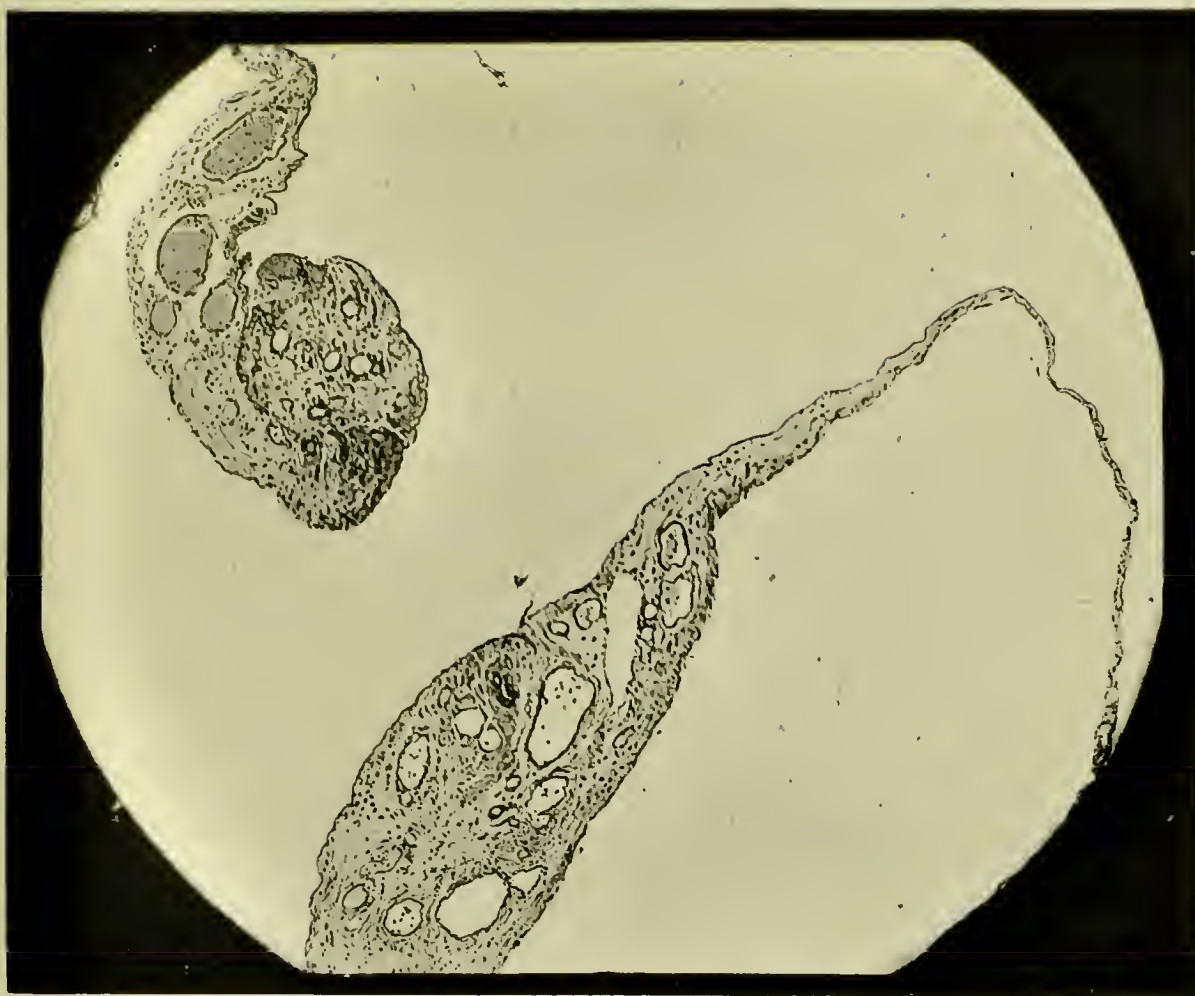


Fig. I.

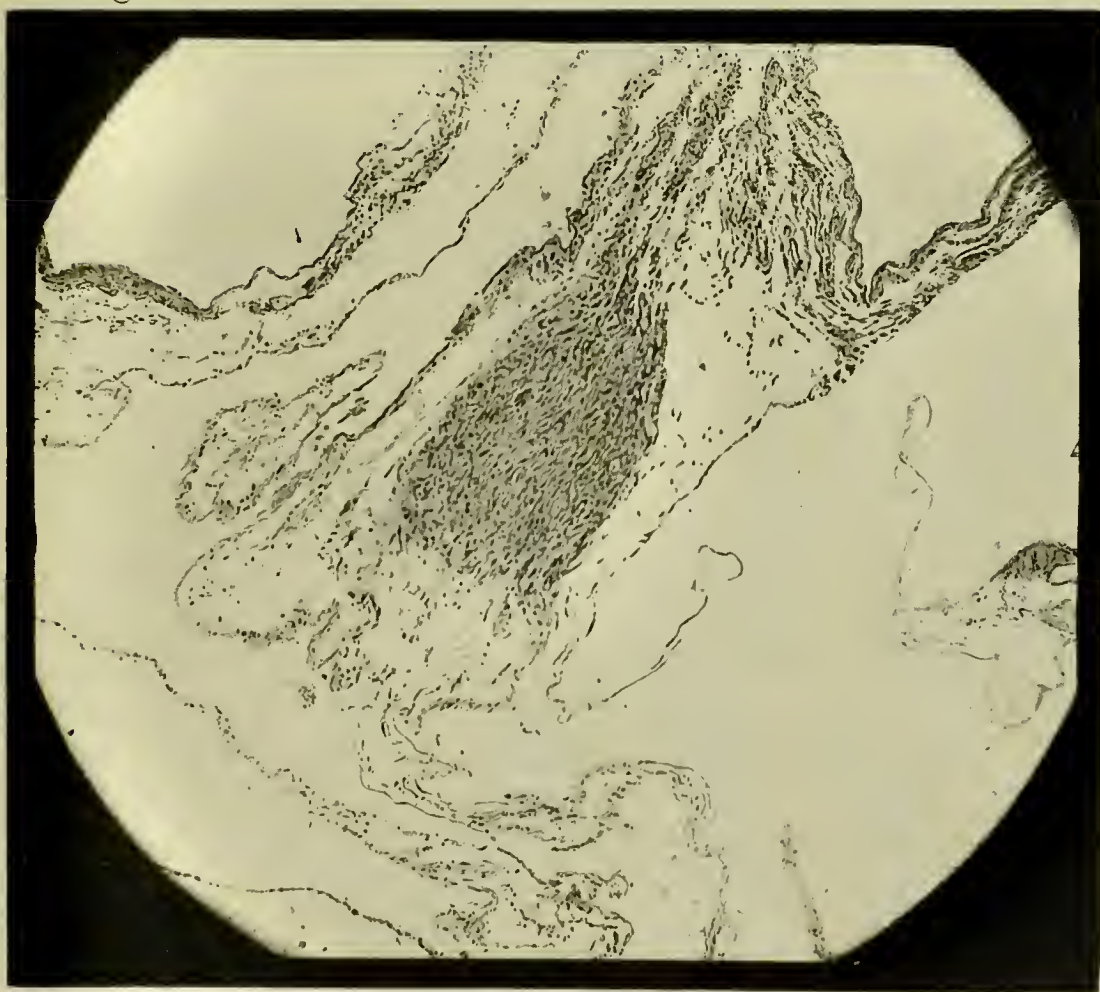


Fig. II.

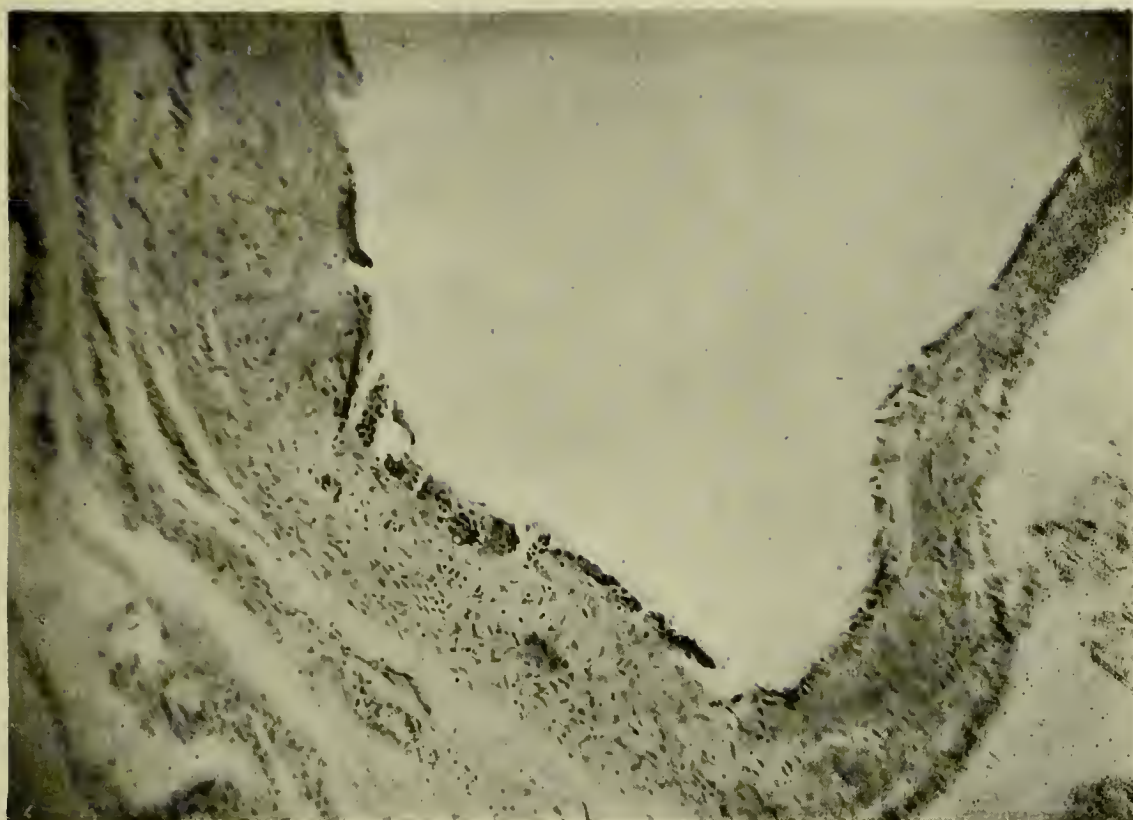


Fig. III.

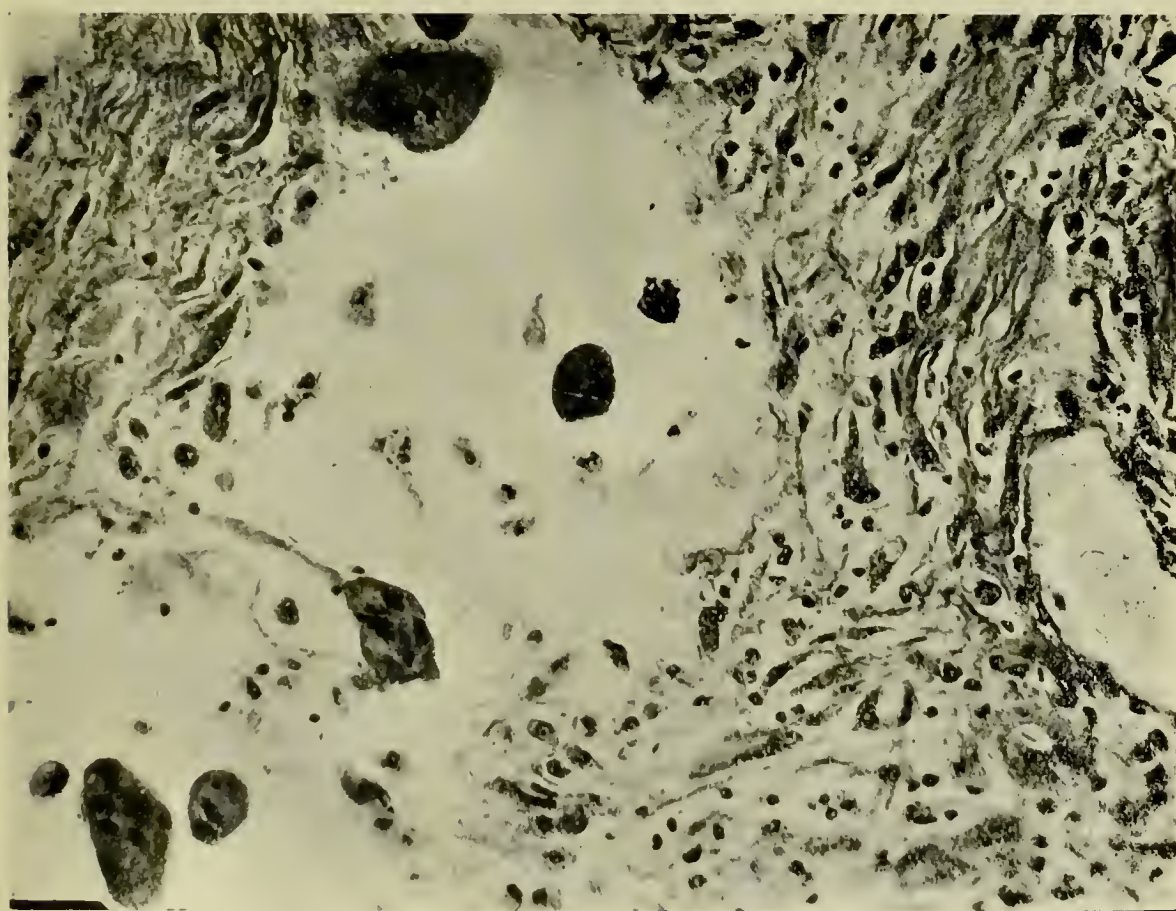


Fig. IV.



Fig. V.

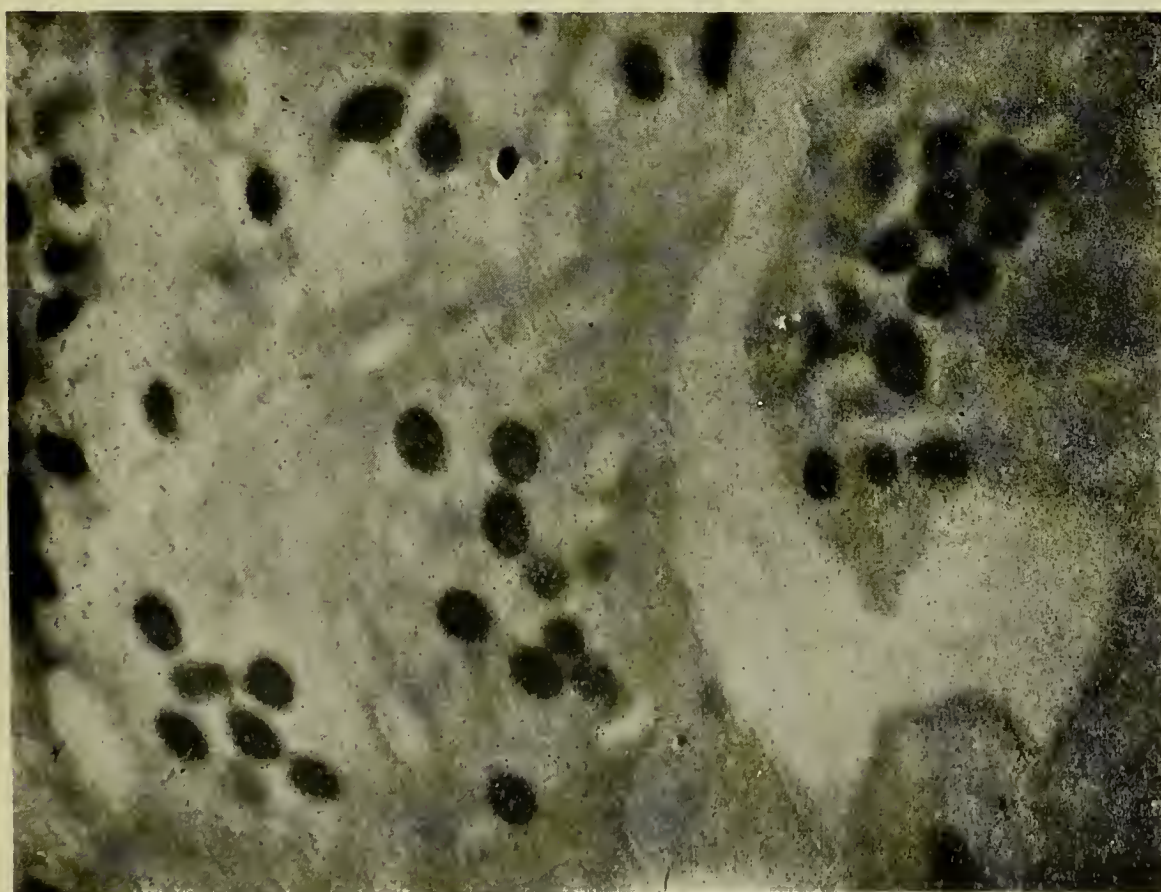


Fig. VI.

detached piece of lung tissue attached by vascular fibrous tissue to the lower border of the left upper lobe. This isolated portion was pale in colour, in marked contrast to the deeply pigmented lung. Although it had no connection whatever with the air passages it was distended with gas. In both of these cases gas must have been secreted from the blood into the detached portion of lung and they are therefore of considerable interest in the present connection.

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DESCRIPTION OF MICROPHOTOGRAPHS.

PLATE I.

Gas-containing cystic tumour of the small intestine removed by surgical operation.
From a photograph; one-third natural size. Mr. Mitchell's case.

Fig. 1. Shows part of the wall of a cyst with large thin-walled blood-vessels; also (top, left) a vascular septum projecting with a free margin into the interior,

at the free margin is a fibrous nodule in which blood-vessels are developing ($\times 45$). Iron Hæmatoxylin and Orange G.

Fig. 2. Shows undifferentiated fibrous nodule and thin cyst walls. ($\times 45$). Iron-Hæmatoxylin, Picric acid, Acid Fuchsin.

Fig. 3. Part of a cyst wall showing lining of multinucleated cells. ($\times 70$). Iron-Hæmatoxylin and Orange G.

Fig. 4. From growing part of tumour. Shows multinucleated cells and proliferation of fibrocytes with separation of the tissues due to gas accumulation. At right side a large thin-walled blood-vessel is seen. ($\times 240$). Safranin, Picric acid, Indigocarmine.

Fig. 5. Shows a very large multinucleated cell with vacuolation and early cyst formation. ($\times 240$). Iron-Hæmatoxylin and Orange G.

Fig. 6. Multinucleated cells from the lining of a cyst showing vacuolation. ($\times 760$). Iron-Hæmatoxylin and Orange G.

NOTE.—Figs. 1, 2, and 4, are from Mr. Mitchell's case; Figs. 3, 5 and 6, from Mr. Thorburn's case.

ON A CASE OF HÆMOLYMPH GLANDS.

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THE attention of those who have investigated the subject of hæmolymp glands has been given chiefly to the question how far these structures are to be regarded as organs essentially different from ordinary lymphatic glands. Some authors have been led by their observations to the conclusion that they are entirely distinct while others have argued that they should be regarded as intermediate between the lymph glands and the spleen and that various forms can be found which when arranged in series show a gradual transition from one type of structure to the other.

Hæmolymp glands occur not only in the human body but in a large variety of animals. They are inconspicuous and, as a rule, are the size of a cherry stone and even smaller. They are often embedded in fatty tissue, as, for example, when they occur in the retroperitoneal tissue of the human body, a site in which they have been frequently observed.

The structure is, generally speaking, that of a lymph gland, a large part of which is occupied by blood sinuses. The presence of blood in these sinuses gives to the tissue a characteristic red appearance and to the naked eye they resemble lymph glands, into which hæmorrhage has taken place. When the sinuses are not so prominent a part of the structure the glands have a marbled grey and red appearance.

The microscopic structure has been described in detail in several papers and I will shortly refer to this subject in giving an account of the present case.

The attempt to define the functions of hæmolymp glands has not so far resulted in definite conclusions. On the one hand they have been looked upon as concerned with the destruction of worn out red corpuscles; but the view has also been adopted that they are composed essentially of hæmogenetic tissue and that both red and white corpuscles are produced by them.

The present case is of interest because of the light which it throws on the nature of one variety of hæmolymp glands in the human subject.

The patient, a woman, aged 25, came to the Infirmary suffering from exophthalmic goitre. The exophthalmos was marked, the action of the heart was very irregular, and there was laboured breathing. She died two days after admission, the only change in her condition being that her temperature had risen to 101.4°F. There was no histological examination of the blood during life.

The summary of the autopsy record is as follows: Thyroid gland moderately enlarged; thymus gland persistent; spleen weighed 13 oz., firm and on the cut surface showing prominent Malpighian bodies; lymphatic glands of the mesentery slightly enlarged and of a pink grey colour. Microscopic examination of them at a later date shewed that they had the structure of ordinary lymph glands but throughout the section were seen large numbers of congested blood-vessels.

The kidneys, the liver, pancreas and intestine were normal; the lungs were normal. There was no disease of the blood-vessels. The heart was dilated and hypertrophied, the myocardium being thickened throughout but especially that of the left ventricle. There was no degeneration in the muscle fibres.

The heart, trachea and larynx with the thyroid gland were removed together in order to retain intact the chain of anterior mediastinal and peri-bronchial lymph glands. These two groups of glands showed the red or marble appearance associated with hæmolymp structure. Many of the glands were markedly increased in size, the largest of them being $1\frac{1}{4}$ in. in length and $\frac{3}{8}$ in. in thickness. The cut surface was red and black in colour, the black being identical in appearance with the pigmentation due to extraneous carbon absorbed from the lungs. In some of the larger glands there were seen on the cut surface circumscribed areas in which the black pigmentation was as abundant as in ordinary glands in this group, while the remainder of the section was red from the presence of blood in the sinuses. After a careful dissection of a few of the individual glands it is apparent that they were supplied by relatively large

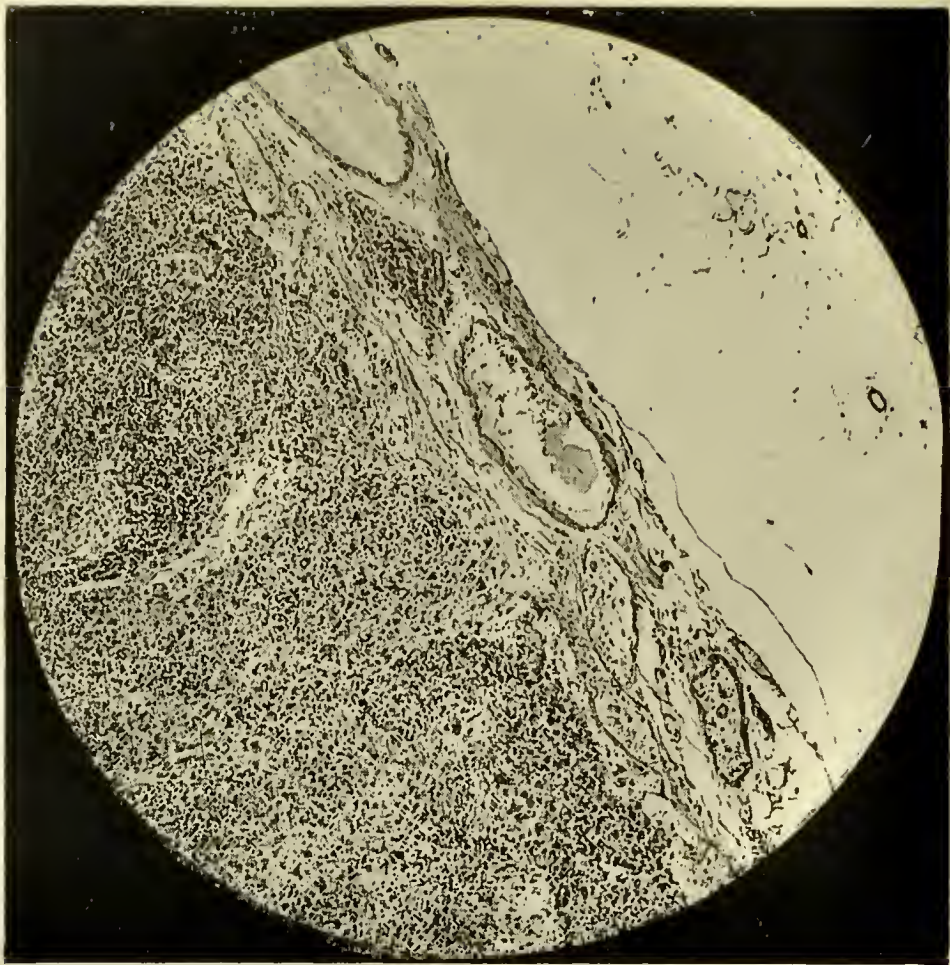


Fig. 1.—Section of gland (low power) showing the capsule in which run afferent lymphatic vessels; subcapsular lymph sinus containing blood; trabeculae passing into the gland from the capsule; peritrabecular sinuses and lymphoid tissue.

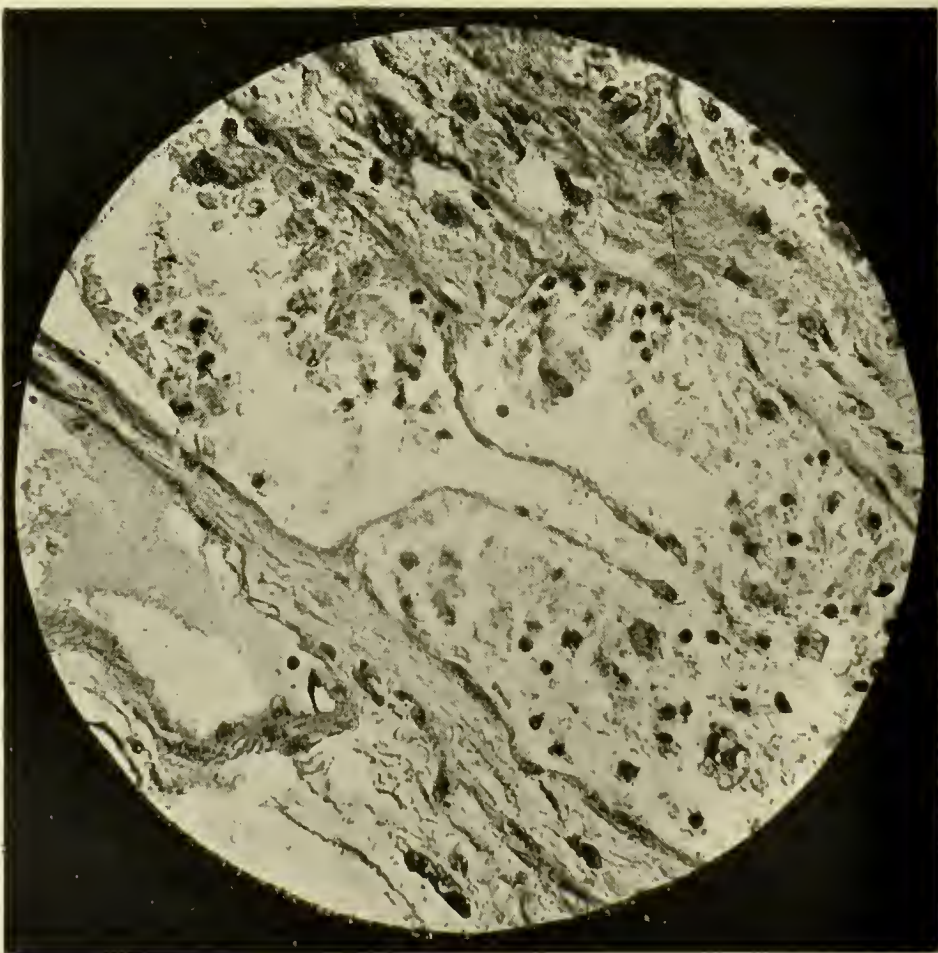


Fig. 2.—Section showing lymphatic vessel in the gland capsule. The valves are seen projecting into the lumen, which contains blood. Amongst the red corpuscles are seen numerous lymphocytes and a few large phagocytes.

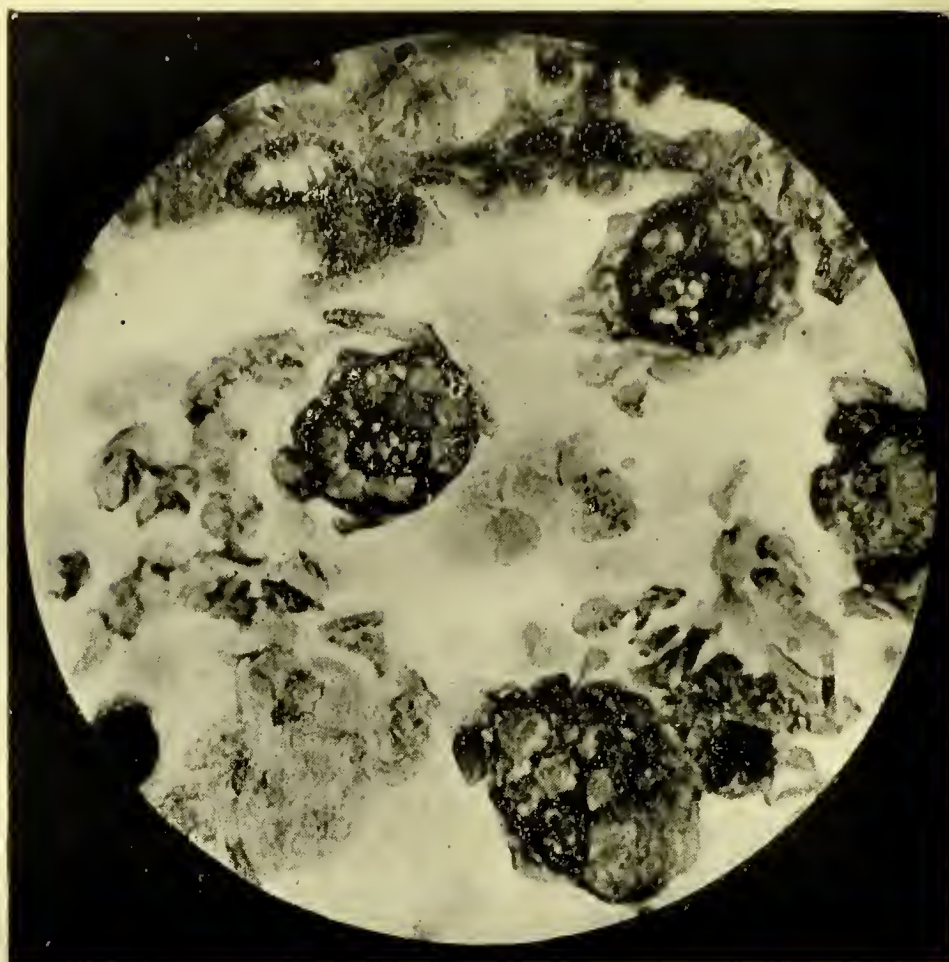


Fig. 3.—Section showing the phagocytes of the lymph sinus; the body of these cells is packed with red blood corpuscles; Zeiss $\frac{1}{12}$ oil immersion.

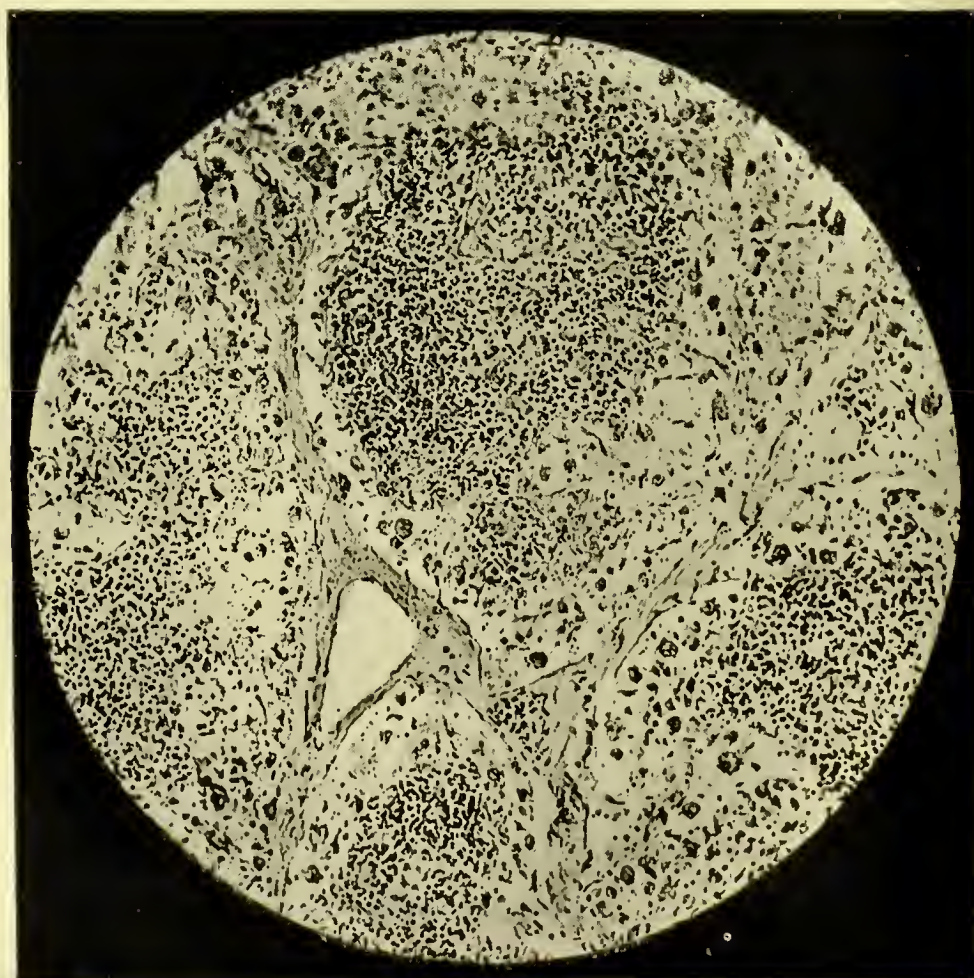


Fig. 4.—Section showing the relation of islands of lymphoid tissue, trabeculae and peritrabecular lymph sinuses containing blood. The conspicuous cells in the sinuses are the phagocytes of the reticulum.

blood-vessels. The veins especially are dilated; but the arterial twigs coming from the internal mammary artery seem also unusually large. The preparation shows also between neighbouring glands the usual inter-communicating lymphatic vessels. In other words these glands have the ordinary anatomical arrangement and also the arterial venous and lymphatic supply of glands in this area.

The microscopic structure of the hæmolymp glands in this case corresponds with that which has been described by various writers. The gland is provided with a capsule consisting partly of fibrous tissue and partly of non-striped muscle fibres. In the capsule on the convex side of the gland may be seen the lymphatic vessels which enter the gland on this aspect (Fig. I.). They can be distinguished by their walls and by the valves (Fig. II.) which are seen projecting into the lumen and pointing towards the gland. These vessels open into the subcapsular sinus and from this communicate directly with the sinuses which are situated alongside the trabeculæ. From the sinus which surrounds the trabeculæ lateral processes extend amongst the lymphoid tissue (Fig. IV.). In all these situations the sinuses are very widely dilated and filled with blood. The blood sinus is separated from the lymphoid tissue by a clearly defined border of endothelial cells but it is impossible to determine whether or not these cells form a continuous membrane. Here and there this border, in place of being a well defined layer of cells, has the appearance of a condensation of the reticulum. Across the sinuses in which the blood is situated there runs a meshwork of fibrous strands on which are situated cells showing comparatively large pale staining nuclei and a moderately abundant protoplasm.

The fibres of the meshwork on which these cells are situated are much thicker than those of an ordinary sinus in a lymph gland. Many of these cells show excessive activity in absorbing into their protoplasm the surrounding red corpuscles (Fig. III.). Occasionally these cells have 2 or 3 nuclei and when the corresponding protoplasm of this plasmodium is packed with red corpuscles the structure forms a very conspicuous globular mass in the field of the microscope. Isolated cells of this type set free

from their original site but still showing the remains of red corpuscles in their protoplasm may be seen in the vessels and spaces which have been described as occurring in the gland capsule (Fig. I. and II.). These free cells occur in blood which contains a relatively large proportion of lymphocytes (Fig. II.) also and we may therefore argue that the blood in these vessels in the capsule has either come from another gland by an intercommunicating lymphatic vessel or has reached the lymphatic vessel by a reflux from the sinuses of the gland into which these vessels are passing. The presence of the valves renders this latter explanation improbable (Fig. II.). It is impossible to regard these vessels in the capsule as other than the afferent lymph vessels of the gland. They enter the capsule on the convex aspect of the gland and communicate with the subcapsular sinuses exactly like the afferent lymphatic vessels of the typical lymph gland. The disposition of the sinuses in the gland and the reticulum which crosses their lumen is also identical with that of the typical gland. The one point of difference which has been clearly made out is that blood occupies the vessels and sinuses which are normally occupied by lymph and that the red corpuscles are being destroyed by the phagocytic cells of the reticulum. The nature of the afferent lymphatic vessels will become clear from a study of the trabeculæ.

The trabeculæ (Fig. IV.) are composed partly of fibrous tissue and partly of non-striped muscle fibres, a fact which can be readily demonstrated by Van Gieson's method. The trabeculæ are mostly much thicker than those of the lymphatic glands from the mesentery, and remind the observer of the clearly defined trabeculæ which are seen in the spleen.

The well defined blood-vessels which run in the trabeculæ are numerous and widely distended with blood. In addition to these, other vessels or spaces are seen with delicate walls composed of a single layer of flat endothelial cells. The relatively large lumen of these vessels is filled more or less completely with a homogenous coagulum which resembles the hyaline thrombus met with in lymphatic vessels. These spaces show occasionally near their walls a series of lymphocytes and polymorphonuclear neutrophile leucocytes and not infrequently a small portion of the lumen is occupied by red corpuscles.

Vessels containing this coagulum can be traced to the hilum of the gland. Here we may observe at intervals along the channel delicate valves which open outwards from the gland. There can no doubt that these channels are the efferent lymphatic vessels which normally pass out from the hilum of the gland. That they are not veins is clear because of their structure and contents. That in this case they contain a small amount of blood is due to the presence of blood in the lymph sinuses.

If we group these observations together it is clear that these hæmolymph glands show the minute structure of ordinary lymph glands and it is further to be noted that the lymphatic vessels which appear in the trabeculæ and which gradually gather into an efferent trunk at the hilum contained lymph which had been to a very large extent freed from the red corpuscles which had found their way into the afferent lymphatics and lymph sinuses. In other words in spite of the apparent change in structure the gland is acting like the ordinary lymph gland in intercepting extraneous particles from the lymph stream. The extraneous matter in this case being the red blood corpuscles.

The sections stained by the Prussian blue method showed surprisingly little evidence of the presence of iron. There was a certain amount of blue staining but much less than one might expect from the amount of phagocytic destruction of red corpuscles which was taking place. Round the nucleus of some of the phagocytes loaded with red corpuscles a blue colour was developed by the application of this method.

The lymphoid tissue consists partly of nodules of small lymphocytes situated in the meshes of a fine reticulum with the characteristic groups of larger endothelial cells in the centre. The remainder of the lymphoid tissue is composed of columns of larger cells with more abundant protoplasm and a round central nucleus which contains relatively less chromatin than the small lymphocytes. The lymphoid tissue as a whole is very vascular and the vessels are markedly congested.

Some of the lymph glands of the mesentery were retained for microscopic examination and for comparison. They showed marked vascularity and congestion. The structure was however that of ordinary lymph glands. The sinuses were free from red

blood cells, the vessels, lymphatics, as well as arteries and veins, were much less prominent, and the trabeculæ were much more delicate in structure. The reticulum was composed of fine fibres and the cells situated on the mesh work in the sinuses were small, round and quiescent. The one point of essential difference was that in the mediastinal glands blood was present in the afferent lymphatics and lymph sinuses. The lymphoid tissue in the mucous membrane of the intestine showed no abnormality. There was nothing to be noted in the section of lung. In the spleen there was a considerable amount of endothelial proliferation and a diminution of the area of the blood sinuses in the spleen pulp. Even after a careful search no evidence of phagocytosis of the red corpuscles in the blood sinuses could be obtained.

The general conclusion to which the study of this case leads us is that the hæmolymph gland is in one form at least nothing else than an ordinary lymph gland into the sinuses of which blood has found its way. How far this conclusion is valid for other cases it is at present impossible to say. According to the records hæmolymph glands have been observed in man and animals singly or in small groups. So far I have not seen another case described in which a well defined group showed this modification generally.

The interesting question remains regarding the meaning of this modification. Nothing has been made out by the investigation to show how the blood reaches the lymph sinuses. The study of the subject by the injection method seems to be by no means free from fallacy. Drummond remarks that after injection it was impossible to distinguish hæmolymph glands from ordinary glands in his experimental investigation. Further information will no doubt be obtained if the search continues amongst well defined groups of lymph glands for the occasional occurrence of this modification.

Apart from the anatomical question as to the channel by which the blood reaches the lymph sinus this case raises one or two interesting questions for the decision of which further observations are required.

In the first place are we justified in regarding the condition

of the spleen in which the blood sinuses were partly obliterated by endothelial proliferation, as in any way connected with the intense phagocytic activity of the reticular cells of the lymph sinus in those glands. Dock and Warthin have observed "hyperplasia by hæmolymph nodes" in cases of the splenic fibrosis of Banti's disease (*Amer. Journ. of Med. Sci.*, 1904). Warthin had previous to the investigation just quoted come to the conclusion that the hæmolymph glands are compensatory structures assuming the function either of the spleen or the bone marrow. The possible connection of the condition with the disease from which this patient suffered should also be kept in view in further investigations.

For an account of the investigation of this subject especially from a comparative point of view with full references to the literature the reader is referred to the recent paper by Weidenreich, *Archiv für Mickros. Anat.*, 1905.

A NOTE ON COLOURLESS FÆCES WITHOUT JAUNDICE.

By J. DIXON MANN,

FOR several specimens which serve to illustrate this contribution I am indebted to my friend the late Dr. Dreschfeld, who took great interest in the subject. Others were sent to me by Dr. Mumford. Most of the observations were made on hospital patients under my care, whose diet could be strictly regulated.

The brown colour of normal fæces is attributed to the presence of urobilin into which the bile-pigment is converted in the intestinal canal; the kind of food also influences their colour. The designation "colourless" fæces is comprehensive: it includes various tints from white to pale grey (sometimes with a faint suspicion of yellow), and those indefinitely tinted stools described as clay-coloured. Occasionally, pale stools quickly acquire a glistening sheen due to a large excess of neutral fat, some of which rapidly congeals on the surface of the fæces after evacuation. When this is associated with a pale, neutral-tinted stool, the motion has a singularly metallic, bronze-like appearance. When the flow of bile is completely obstructed, as in total blockage of the common duct, the fæces are devoid of natural pigment and, if the diet of the patient is restricted to milk, they will be quite colourless. It is to be observed, in severe jaundice, that a mere trace of bile may find its way into the bowel without the urobilin it furnishes being sufficient perceptibly to colour the motion, especially as such motions usually contain a large amount of fat which obscures any slight coloration that is present. When absolute blockage of the common duct occurs, it is probable that small amounts of absorbed urobilin may be excreted through the walls of the intestinal canal. Cases of stoppage of the bile with concurrent jaundice, however, are distinct from those under consideration which are limited to cases that are free from jaundice and from any obstruction to the flow of bile into the duodenum.

The reduction of bilirubin into urobilin is due to bacterial

action; it takes place in the cæcum and in the upper part of the large intestine; exceptionally, it may take place in the lower part of the small intestine, and is then probably pathological. When urobilin is formed in the small intestine, it is absorbed with great activity and consequently appears in excessive amount in the urine. The reduction of bilirubin may be carried beyond the stage of urobilin-formation, and then a colourless body—urobilinogen—the chromogen of urobilin, is formed. In this way, although a normal amount of transformed bile-pigment may be present in the fæces, they may be devoid of colour. Urobilinogen is readily oxidised by sunlight and air, and is thus converted into urobilin. If colourless fæces which contain urobilinogen are exposed to the air, they develop colour which in time becomes brown. The specimens of fæces which were examined were voided in the dark and were at once enclosed in well-corked earthenware vessels in order to avoid premature conversion of urobilinogen into urobilin.

A specimen, which was slightly tinted stone-colour, had a feebly acid reaction, and darkened on exposure to air. An alcoholic extract gave a negative reaction for bilirubin. It showed a feeble urobilin-spectrum and a faint fluorescence with zinc acetate. A few drops of tincture of iodine were added to some of the extract which was then allowed to stand for a short time. On re-examination, the urobilin band was found to be much denser, and the fluorescence more intense. The inference is that the fæces contained a small amount of urobilin along with a considerable amount of its chromogen which accounted for the darkening on exposure to air, and for the increase of urobilin when the urobilinogen in the alcoholic extract was oxidised by the addition of iodine. Another specimen from the same patient, obtained two months later, had much the same colour, but it was alkaline in reaction; it also darkened on exposure. An alkaline extract contained neither bilirubin nor urobilin. The darkening on exposure pointed to the presence of urobilinogen which was identified by means of Ehrlich's para-dimethylamidobenzaldehyde test. This reagent does not react with urobilin, but it reacts with urobilinogen, and also with indol and skatol, so that it is necessary to free the

fæces from these bodies before using it as a test for urobilinogen. A portion of the fæces was repeatedly extracted with petroleum-ether, after the method of Otto Naubauer, by which the indol and skatol are removed, along with some of the fat; the extraction (which is a tedious process) was continued until the petroleum ceased to react with the benzaldehyde. An alcoholic extract of the fæces after they had been thus dealt with gave a brilliant red colour with Ehrlich's test, which yielded the characteristic absorption band close to the right of the D line. On oxidation, the extract gave the reactions of urobilin.

Formerly, the presence of great excess of fat was supposed to account for the occurrence of colourless fæces without jaundice; in some instances, excess of fatty matter undoubtedly has a considerable influence in this respect, but it is rarely the sole factor. One of the specimens placed at my disposal by Dr. Dreschfeld illustrates this. It had a very pale *café au lait* colour; it was of creamy consistency and had an alkaline reaction. On rubbing some of the fæces in a mortar with petroleum-ether, they at once darkened considerably, and the petroleum became opaquely white, like milk. These fæces contained a less than normal amount of urobilin which was obscured by excess of fat.

A specimen from a hospital patient showed a condition which is occasionally, but not often met with. The patient suffered from stricture of the lower bowel for which she subsequently underwent an operation. At the time she was chiefly on milk diet. Nothing noteworthy was observed about the fæces until my attention was called to an evacuation which was white; it had a sour odour like strong cream cheese, and a freely acid reaction. There was no jaundice, nor was the urine darkened in colour. On exposing a layer of the fæces on the water bath, they slowly acquired a very pale buff-tint, which did not deepen after prolonged exposure to air. An alcoholic extract contained neither bilirubin nor urobilin. After being exhausted with petroleum-ether, the fæces gave no reaction with Ehrlich's benzaldehyde test, nor with Schmidt's sublimate test. The acidity was chiefly due to butyric acid. Microscopical examination showed abundance of neutral fat, with clumps of soaps and

clots of casein. Here, it is probable that no bile-pigment had reached the intestine whilst this motion was in progress, and yet there was no jaundice. Although the urine was not bile-stained, an extract obtained from a considerable quantity yielded evidence of a trace of bile-pigment, but no urobilin was present. On the following day the motion was moderately dark in colour, and it contained both bilirubin and urobilin. In this case it appears probable that the flow of bile was abruptly and completely arrested for several hours, and then as abruptly restored. The patient had no pain as of gallstone, nor was any stone found in the subsequent motions, nor at the operation. It is interesting to note that on the sudden reappearance of the bile, some of the bilirubin passed along the bowel unchanged.

The assumption of a temporary stoppage of the bile, however, does not account for all the cases of colourless fæces which do not darken on exposure. Instances occur in which the condition persists for many consecutive days without the least trace of jaundice. Cases of this description are difficult of explanation on the lines at present accepted relating to the pigment of normal fæces. I have long felt convinced that the presence or absence of urobilin does not account for all the variations in fæcal coloration, and am disposed to believe that other unrecognised pigments (apart from the colouring matter of food) contribute towards it. A still more heterodox opinion has recently been expressed by Steensma (*Ned. Tydschr. v. Geneesk.*, 1907) who believes that there is no urobilin to speak of in normal fæces immediately after they are voided, only urobilinogen. He holds that the colour of normal fæces does not depend upon urobilin; as alcoholic extracts of acholic, and of normal fæces, show no appreciable difference in colour.

The pathological conditions in which colourless fæces without jaundice may occur, comprise defective supply of bile to the duodenum, intestinal catarrh, tuberculous abdominal disease, malignant disease of the intestine, septic diseases (especially those which affect the abdomen), chlorosis, and leukæmia.

CASE OF (?) TUBERCULAR INTRA-OCULAR GROWTH.

By A. HILL GRIFFITH, M.D.,

Ophthalmic Surgeon, Royal Infirmary; Surgeon, Royal Eye Hospital; Lecturer on Clinical Ophthalmology, Victoria University of Manchester.

THE case came under my charge some nine years ago at the Royal Eye Hospital, and as I have never before or since seen any case quite similar I am taking this opportunity of recording it.

Elizabeth J., aged 22, single, farm servant, was first seen by me as an out-patient on June 22nd, 1898. The right eye was quite blind, the pupil reacted through the other eye only, the tension was normal and there was no redness or other changes to be seen. She had a blow on the eye some months before and the (?) sight failed since.

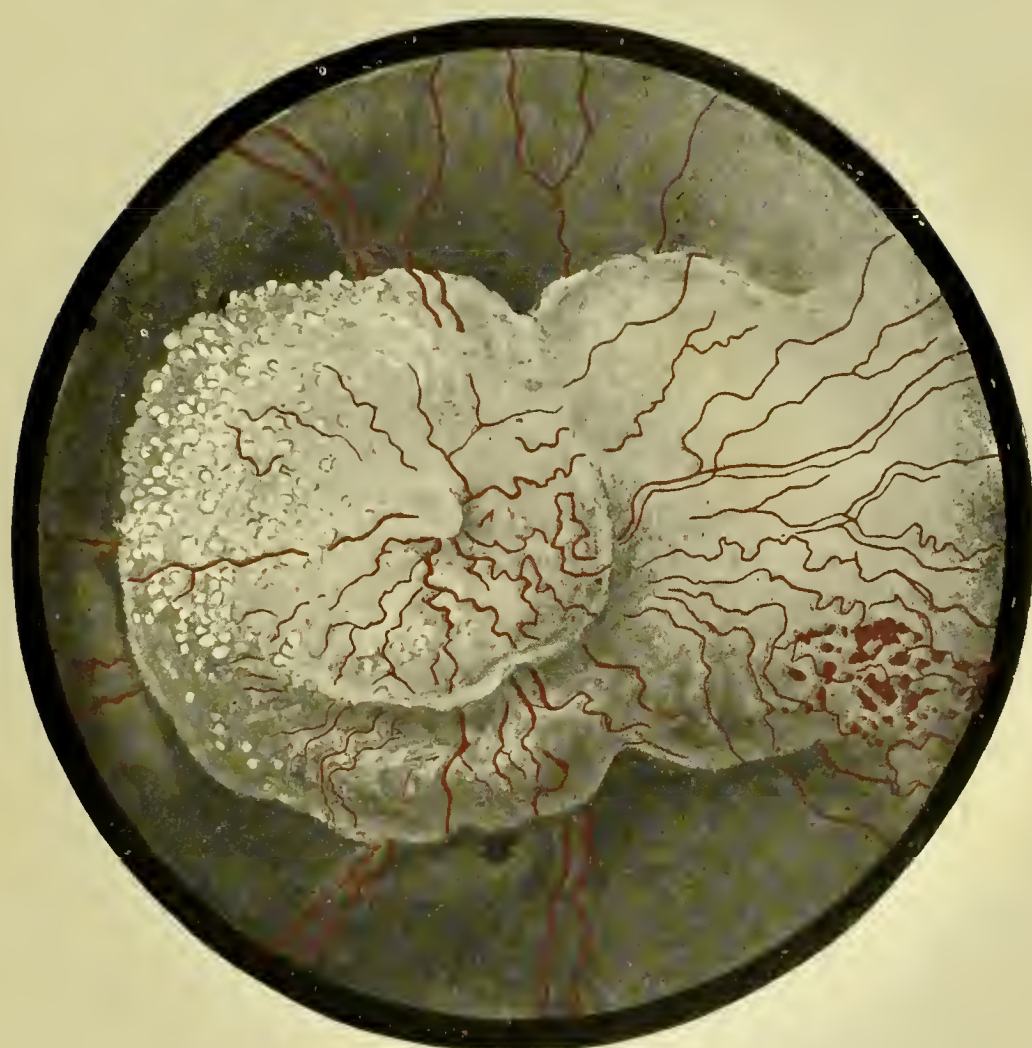
The sight of the other eye has also quite lately failed somewhat, the vision is $\frac{6}{12}$, the disc rather pale, chalky in appearance, and "filled in," the vessels are rather small. The chart of the visual field shows a large defect at the nasal side.

Her father died of heart disease; her mother, aged 60, is alive and healthy, one brother aged 32 is well, one sister aged 27 is also healthy, one other sister died from fits the sequence of a severe blow on the head.

Patient has had severe frontal pain for last few weeks, and also complains of staggering at times, especially on rising up. She had rheumatic fever when a small girl, but no rheumatism since. Her occupation necessitates long hours and hard manual labour making cheeses, etc. There is some glandular swelling on the right side of neck.

Dr. R. T. Williamson kindly examined her and found the lungs, heart, etc., all normal.

She was admitted as an in-patient and remained in the Hospital three weeks, during which time the eye and general



condition were repeatedly examined by myself and others, but nothing further was made out.

The ophthalmoscopic appearances of the growth in the right eye are well depicted in the accompanying drawing which has been very successfully done by Dr. W. E. Fothergill.

The disc and a large area in the centre of the fundus is occupied by a rounded mass like a dense fleecy thunder-cloud, over which can be traced the retinal vessels.

The outer half forms a sharply defined steep rounded swelling, extending well forward into the vitreous. This portion is slightly translucent and its surface is thickly covered by round shining refractive bodies somewhat resembling drops of oil or fat. These little white tufts scattered over the growth can be seen in places against the sky line as it were and the appearances reminded one of a bare hill with a flock of sheep on it.

The inner half of the growth is not nearly so prominent, steep or sharply defined, but gradually shades off to the level of the choroid. This portion is nearly free from the above mentioned white tufted bodies but shows a few hæmorrhages.

The treatment consisted in the administration of cod liver oil and creosote.

The patient was 12 months later re-admitted as an indoor patient and remained under observation for four weeks.

The appearances of the growth were practically unchanged, but the vitreous, which before was noted as clear, showed a few fine filamentary opacities. Eye externally quite normal and tension of globe was normal. The sight of the left eye was now quite normal.

The patient says that the sight of the bad eye has been failing for five years, and I think this is much more likely to be correct than her former statement.

Tumors in the fundus are not common and practically speaking are of three different kinds: glioma of the retina, sarcoma of the choroid and tubercular masses. One must also mention adenoma, angioma, fibro-chondroma, metastatic carcinoma, and some other even rarer growths.

In dealing with our case one can exclude glioma from the

age of the patient. Carcinoma is always secondary and for this and other reasons can be also definitely put aside. The appearances are totally different from any other case of sarcoma I have ever seen and I have seen a good many.

At the December, 1891, Meeting of the Ophthalmological Society, Johnson Taylor showed a patient with "A growth of a doubtful nature," the features of which somewhat resembled our case, but there were no globular bodies. There had been marked impairment of vision for eleven years.

The eyeball having been removed some eighteen months later, the growth proved to be a spindle-celled choroidal sarcoma somewhat cavernous in structure.

It is possible that our case may, like the above, be some anomalous form of sarcoma.

On the whole I am inclined to regard it as tubercular but I am by no means certain, and as I cannot trace the patient the diagnosis must remain unsettled.

CHRONIC JOINT DISEASE OF STILL'S TYPE.

By E. N. CUNLIFFE, M.D., M.R.C.P.

Honorary Assistant Physician, Royal Infirmary, Manchester.

It has been recognised for many years that occasionally children suffer from chronic disease of the joints resembling, more or less closely, rheumatoid arthritis of the adult and such cases have been grouped indiscriminately together as cases of rheumatoid arthritis. Still in 1896 read a paper¹ before the Royal Medical and Chirurgical Society of London, in which he showed that several distinct joint affections had been described as belonging to this group and he emphasised the importance of further differentiation. He suggested that there were at least three quite distinct joint affections included in this group. One of these is extremely rare and is not allied to rheumatoid arthritis of the adult in any way. Its etiology and pathology are probably identical with those of acute rheumatism. There is no evidence of bony change and the deformities that are met with are due to the invasion of neighbouring tendon sheaths by a process of fibrosis originating in the structures surrounding the joints. Other rheumatic manifestations, such as heart disease or subcutaneous nodules, may be present and Still suggested that the term "chronic fibrous rheumatism" was the best one to apply to this condition. The second class of case met with, very closely resembles rheumatoid arthritis of the adult and clinically at any rate it appeared to be identical with that disease. It comes on after the second dentition, is polyarticular and the usual deformities and osteophytes occur, as in rheumatoid arthritis of the adult. To this form of chronic joint disease in children the term "rheumatoid arthritis" should be restricted. Much more frequent than either of these two varieties, is a form of chronic disease, possessing distinctive characters, that entitle it to be recognised as a clinical entity, and since we are indebted to Still for the differentiation of this important group of cases, it is convenient to apply to them the term "Still's disease," at any rate temporarily, until the pathogenesis of the disease is

more clearly defined. Several cases of Still's disease have been described since 1896 but the disease seems sufficiently rare to justify the publication of the details of even an isolated case. A clinician of such wide experience as the late Dr. Dreschfeld had only seen one example of the disease, and a melancholy interest will always be attached in my mind to the case I am now reporting, in that the last conversation I had with my old teacher, a day or two previous to his death, was in reference to this case and he showed all that enthusiastic interest that made association with him so stimulating and helpful to others, and promised to see my patient on his next visit to the Hospital.

Still's disease may be defined as a chronic progressive enlargement of the joints, associated with enlargement of lymphatic glands, and usually of the spleen. The essential characters of the disease will be readily understood from the details given below.

Edith J., aged 11 years, was admitted to the Manchester Royal Infirmary, under my care, on June 17th, 1907, complaining of inability to walk on account of stiffness of the knees and ankles. The onset of the disease dated back two years, when the right knee gradually became swollen, no complaint being made of pain. About the same time the right ankle also swelled, and the patient limped in the right leg, walking on her toes. Six months later, the left knee and ankle became affected with swelling, pain again being absent. In August, 1906, she was admitted to the Children's Hospital, Pendlebury, under Mr. C. Roberts, to whom I am indebted for the notes of her condition at that time. The right knee was held in a flexed position, and there was very little movement. There was no tenderness. The knee was swollen and fluctuation was obtained on the inner side. The right ankle was also swollen and rigid. The left knee and ankle were similarly affected, but to a less extent. The left hip was flexed and slightly abducted, and there was marked lordosis. The joints of the upper extremity were unaffected. Walking was impossible owing to the stiffness of the knees and ankles; on three occasions the joints were moved under an anæsthetic, with the result that, by means of crutches, walking was possible for a time, but patient very



rapidly relapsed into her former condition. The forcible movement of the joints was sometimes followed by effusion. She continued under observation at Pendlebury Hospital till November, the only feature of interest being the occasional occurrence of night cries. Soon after her return home, both wrists began to be affected, swelling and limitation of movement developing, without pain or redness.

Previous Medical History. Patient suffered from measles and mumps in infancy, from scarlet fever in 1902, and from chicken-pox in 1903. These diseases apparently ran a mild course without complications. Apart from the acute specific fevers, patient had a clean bill of health, and attended school regularly till the age of nine years.

Family History. No history of tuberculosis or rheumatism.

Condition on Admission. She is a bright, intelligent girl. The face is pale, but not wasted. The right pupil is considerably smaller than the left, but her mother tells us that such has always been the case. There is slight but distinct hemiatrophy of the face on the left side. The trunk is well-developed and well-nourished. Patient is completely bedridden, due to the fixation of the joints of the lower extremity.

Knee Joints. Both knees are swollen. The affection is markedly symmetrical. The legs are flexed at right angles on the thighs, and movement is slight on the left side and almost imperceptible on the right. There is no pain or tenderness of the knees, except on attempts at movement. The swelling seems chiefly confined to the soft structures, and examination by the X-rays show no bony changes. The ankylosis is evidently due to contraction of fibrous and tendinous structures around the joints. There are no signs of free fluid. One of the most striking features of the condition is the marked muscular wasting of the thighs and legs. The tendons of the hamstring muscles stand out under the skin as taut bands.

Ankle Joints. Affected similarly to knees.

Wrist Joints. The left wrist is more affected than the right. The dorsal and palmar aspects of the carpus are markedly swollen, obliterating all normal depressions. The swelling is soft and pulpy, and closely resembles the "white swelling" of

a tuberculous joint. Movement is restricted, but still possible; there is some tendinous creaking on movement. X-rays show no bony changes.

Hands. The metacarpo-phalangeal joint of the right thumb is affected, and the similar joint of the left index finger.

Elbows. Not much affected. There is some restriction of supination and pronation on the left side, and the arm and forearm muscles are considerably wasted.

Hips. Right hip apparently free. Left hip shows partial ankylosis with limited external rotation. There is no lordosis, however.

Other Joints. Apparently unaffected. Spinal column shows no signs of disease.

Lymphatic Glands. The cervical glands, especially those in the posterior triangle, are enlarged on both sides but more markedly on the left. The axillary, supratrochlear and inguinal glands are also enlarged. The glands are separate, rather hard, not tender and vary in size from a pea to a hazelnut.

Spleen. Not palpable and no apparent increase, as determined by percussion.

Tonsils. Not enlarged.

Heart. No evidence of valvular disease or of adherent pericardium.

Lungs. No signs of tuberculosis or pleurisy.

Temperature. Periods of apyrexia, alternating with short periods of pyrexia, but evening temperature never greater than 100°.

Blood. Moderate amount of anæmia. Hæmoglobin decreased to 80 per cent; red cells normal, white cells decreased, with relative lymphocytosis.

Urine. Apparently normal.

Course of the Disease. During the six months patient remained under my observation, very little change occurred. The right elbow gradually became affected and it was interesting to note the entire absence of pain, redness and effusion and the insidious onset of stiffness and swelling, apparently due to extra-articular fibrous changes.

Treatment. The advisability of surgical procedures was considered, but Mr. Wright, who kindly gave me his valuable opinion on the case, agreed that it was better not to run the risk of stirring up active mischief by forcible manipulations under an anæsthetic. General tonic treatment was instituted with good effect on the general condition of the patient. Locally massage was employed and extension by weights was successful in correcting some of the deformity due to flexion of the knees but our patient was still unable to walk when she left hospital. Dr. Loveday kindly made a series of observations as to the opsonic index of the blood to the tubercle bacillus and injections of tuberculin were employed and Bier's treatment by passive congestion was tried, at Dr. Loveday's suggestion, the method being used at those times when the opsonic index was high. The opsonic index determinations will be referred to at more length when the discussion of the nature of the disease is considered. It will be sufficient to state here that the local improvement under these measures was extremely slight and our patient left the hospital with her general health improved but the local joint condition not distinctly ameliorated.

Diagnosis. There seems no doubt that the condition was an example of the polyarthritis, originally described by Still. The age of onset was a little later than in Still's cases² where, out of twelve cases, ten began before the second dentition. Enlargement of the spleen is not always noted; it was found by Still in nine out of twelve cases. Parkes Weber³ describes a case very similar to the present one commencing in a girl at twelve and a half years.

Nature of the Disease.

The clinical appearances and pathological findings alike negative the idea that Still's disease is related to osteoarthritis. Fibrillation of the cartilage, osteophytic change, and exposure and eburnation of bone were all absent in the three autopsies recorded by Still.² This author thinks the pathology of the disease uncertain, but that some of the symptoms are at least suggestive of a microbic origin. Parkes Weber⁴ has described a case of Still's disease where an attack, of what was apparently endocarditis, occurred, and since pericardial adhesions

have been found in other cases, he was inclined to believe that the affection was more allied to articular rheumatism than to any forms of osteo-arthritis met with in adults. Poynton and Paine attempted to obtain microbic cultivations from the joints of Parkes Weber's case, but the attempt failed. In the discussion which followed the reading of Parkes Weber's paper before the Medical Society, Sansom was of opinion that the arthritis was not one of rheumatic origin, and he thought there was no definite evidence of endocarditis; and Cautley, Rolleston and Morison were also of opinion that rheumatism could not be regarded as the cause of Still's disease. Poynton, however, quoted two cases observed by him which seemed to point to a rheumatic origin. Parkes Weber in a later paper⁵ referred again to the case mentioned above, which he had kept under observation, and was still of opinion that the original affection had been, or at all events had been complicated with, a form of true rheumatism.

Most authorities are, however, distinctly against this view of the rheumatic origin of Still's disease, and Parkes Weber, in a still later paper,³ inclines to the view that tuberculosis is concerned in its production, most probably by the absorption of toxins formed by tubercle bacilli developing elsewhere. The arthritic manifestations of tuberculosis have received considerable attention at the hands of French observers. Poncet,⁶ in an article on "Tuberculous Rheumatism or Pseudo-rheumatism of Bacillary Origin," gives several instances of adults suffering from tuberculosis of the lungs complicated by chronic disease of the joints, resembling, from the description given, in some cases osteoarthritis, in other cases the lesions occurring in Still's disease, and in one instance inoculations showed the presence of tubercle bacilli. In a later paper⁷ he describes a case of "senile morbus coxæ," which he believed to be due to "tuberculinisation," that is, poisoning by the tubercular virus rather than infection by the bacillus. He quotes the experiments of D'Or and Courmant, who succeeded in producing serous fungating arthritis with no bony changes by the intravenous injection of attenuated tubercle bacilli. Mouriquand⁸ relates a case of "infantile tuberculous rheumatism," which apparently corre-

sponds to Still's type of polyarthritis, and is of opinion that the symmetrical nature points to a toxin secreted at some distance by the tubercle bacillus. Mailland,⁹ in a paper on "Primitive Tuberculous Rheumatism," is of opinion that what looks like a rheumatic arthropathy may be due to tuberculosis, and is not necessarily progressive, but may disappear with the appearance of typical tubercular lesions elsewhere in the body. In other cases a progressive, plastic, ankylosing arthritis may result. Patel¹⁰ thinks that tuberculous rheumatism is much commoner in children than in adults. Johannessen¹¹ reports a case of chronic joint disease commencing in a girl at the age of four years, symmetrically involving the feet, knees, elbows and hands, where later pulmonary tuberculosis developed. There is, therefore, abundant evidence to prove that a chronic disease of the joints, apparently similar to that occurring in Still's disease, may arise in the course of tuberculosis. Further evidence in favour of the tubercular nature of Still's disease is furnished by the results of tuberculin injections. Parkes Weber³ found that tuberculin caused a positive reaction generally, but no local reaction, and was inclined from this evidence to believe that the joint condition was not due to direct invasion by the bacilli. Edsall,¹² however, found that tuberculin injections reacted positively each time, but joint pains accompanied the general reaction. I thought it would be of interest in the case I had under observation, to have the opsonic index to the tubercle bacillus estimated, and the reactions to tuberculin inoculations considered, in the light of A. E. Wright's recent work. I had the advantage of Dr. Loveday's skilled help in this, and I am indebted to him for the following report:—

"The patient's opsonic index was determined with the view of the possibility of the condition being tuberculous. The tubercular opsonic index was .66 which, although not an absolute proof of a tubercular infection being present, is strongly suggestive when the excellent general condition of the patient is borne in mind. Inoculations of $\frac{1}{2000}$ m.g. tuberculin were given on June 28th, 1907, July 8th, 1907, and on August 9th, on her return from the Convalescent Hospital at Cheadle. In every case a decided reaction followed. Thinking that smaller

doses could be used, she received in succession three doses of $\frac{1}{4000}$ m.g. and in each case again the reaction was positive. The doses given were calculated on the assumption that 1 c.c. T.R. contains 10 m. gms. tubercle powder.

The indices were as follows :—

June 27.—·26.

July 8.—(10 days after $\frac{1}{2000}$ mg. inoculated) 1·12.

„ 11.—·75.

„ 18.—1·16.

„ 22.—(4 days after $\frac{1}{2000}$ mg. inoculated) 2·51.

Aug. 8.—·85.

„ 15.—(4 days after $\frac{1}{2000}$ mg. inoculated) 1·00.

„ 19.—1·35.

„ 29.—1·39.

Sept. 5.—·87.

„ 9.—(3 days after $\frac{1}{4000}$ mg. inoculated) 1·41.

„ 16.—1·00.

„ 23.—·92.

„ 26.—(2 days after $\frac{1}{4000}$ mg. inoculated) 1·16.

Oct. 14.—·79.

G. E. LOVEDAY.”

These observations clearly point to tuberculosis having an important part in the production of the joint changes found in Still's disease. The question as to whether the changes are due to direct invasion of the joints by the tubercle bacillus or due to the action of a toxin produced by the tubercle bacilli settled in some other nidus, is more difficult to decide. The observations of the French observers quoted above, seem to me, however, to be strongly in favour of the view that tubercle bacilli are actually present in the joints. The low tubercle opsonic index observed when my patient first came under observation points, moreover, rather to some local tubercular infection than to a general toxæmia, which one would expect to raise the opsonic index. It is possible, of course, that we have to deal with a mixed infection since the joint lesions are not unlike those met with in cases of “absorption arthritis.” There was no evidence in my case of any source of septic infection but in

any other examples of this disease that may come under my observation, I shall certainly have the opsonic index to the commoner septic micro-organisms determined.

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E. N. CUNLIFFE.

BLOOD PLATES.

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THIS short paper is merely a preliminary note on some observations on blood platelets which I have been carrying out in the clinical laboratory of the Manchester Royal Infirmary and in the private pathological laboratory of Prof. Lorrain Smith, in the University of Manchester, for the past two years. The work is still very incomplete, for apparently the appearance of platelets in blood may have very wide physiological and pathological bearings. Very much work has been previously done on the same subject, but I do not propose to review this here. I will simply give a short account of my own line of observation.

NORMAL BLOOD.

Technique. In carrying out the following observations a regular and definite mode of procedure was always adopted. A finger or ear was pricked without any previous cleansing precautions more than washing with soap and water, and the slide, previously cleaned with chromic acid and alcohol and dried, gently touched on the surface of the drop of blood which exuded from the puncture. A cigarette paper was used for smearing. This was dipped into the blood on the slide, so that the blood diffused across the whole breadth of the paper; the paper was then allowed to fall on the line of blood so that it was slightly gripped and required a small amount of force to pull it along and make the smear. This method gives very good uniformly distributed smears without any special collection of white cells at any part of the smear. It has its objections, I know, but it also has its advantages, and to these are due in great part the results of my experiments. The slide was then allowed to dry in the air. When ready it was rapidly flooded with 5 or 7 drops of

Leishman's stain and then allowed to stand so for 15—30 seconds, according to the thickness of the film. Twice the bulk of filtered water or a soft tap water, like Manchester water, was then added to the stain on the slide, and the dilute stain allowed to act for five minutes. The slide was then well rinsed with the same water, and allowed to stand moist for one minute, roughly dried with filter paper, and then waved gently over a small bunsen flame until all traces of moisture had disappeared. The preparation was now ready for examination with an oil immersion lens, but I always preferred to mount in Canada balsam and cover with a thin glass slip, care being taken to get the very edge of the original seat of the blood drop under the cover-slip, as it is at this region that the platelets are most prevalent.

I have used no other chemical reagents in these observations than what are contained in Leishman's stain, soft (Manchester) tap water and very occasionally distilled water. A few of the slides were warmed to temperatures hotter than that of the body before the drop of blood was transferred to them, but most of them were warmed to body heat, or used at the temperature of the room worked in. The cigarette paper seems to me to do less injury to the blood elements, especially after they have stood 20—30 seconds, than does a glass slide when such be used for making the smear. Thus, the latter procedure breaks up the red corpuscles very readily, forming more or less homogeneous masses of confluent red cells, whilst a cigarette paper does little apparent injury to them; a glass side also appears to injure the platelets and to remove an important part of their substance from them.

Situation of the blood plates. The blood plates always appear in most profusion on that part of the slide on which the drop of blood is put before the smear is made. This effect is more intensified if, instead of just touching the drop of blood on the finger with the slide, the slide be moved whilst touching the drop of blood so that a streak of blood about one-quarter to half-an-inch long is transferred to it. Very few platelets, comparatively speaking, are to be found in the rest of the smear. When the smear is made most successfully the cigarette paper wipes away the bulk of the red cells from the original seat of the

drop or streak of blood, so that to the naked eye this first portion of the smear is devoid of red cells, and looks apparently as if no blood were left there. When the slide is, however, examined after staining, in this apparently clear part of the smear blood plates in great profusion are found, with a few red and white cells scattered about. (See Fig. 1, low power Zeiss A.)

Conditions affecting the formation of blood plates. The number of platelets which appears on a slide made in the above way increases with the length of time, within certain limits, which elapses between the contact of the drop of blood with the slide and the making of the smear. Thus there are more platelets after 10 seconds than after immediate smearing, more again after 20 seconds, and most after 30 seconds interval between the parts of the process of making a blood smear. The platelets appear better still if in addition to the above conditions the slide has been warmed to about body heat before the blood is transferred from the seat of puncture to the glass. This may be on account of the heat fixing the platelet so that it stands the further manipulations better. If the slide be made hotter still, but bearable against the cheek, the platelets form more rapidly. If the slide be made hot as in the last case, and the cigarette paper or the glass smearing slide be drawn through the drop of blood and then smeared on the hot slide, the platelets are distributed better in the body of the smear, and do not collect at the first portion of it.

If the blood be allowed to stand more than 30 seconds on the cold or warm slide before the smear is made the platelets are inclined to alter in characteristics and to be not so well formed.

If the blood be allowed to stand 60 seconds it is difficult to smear, and no good platelets are to be seen. In such a slide, if the red cells be gently washed off with a stream of water and the slide dried gently over a flame, and the then residue treated with Leishman's stain, a network of fibrin with multipolar bodies at the intersection and continuous with the fibrin are seen. The multipolar bodies are not like the blood plates, and there are none of the latter to be found. This suggests that the platelets play some part in the formation of the network of fibrin which is such an important feature in the coagulation of blood.

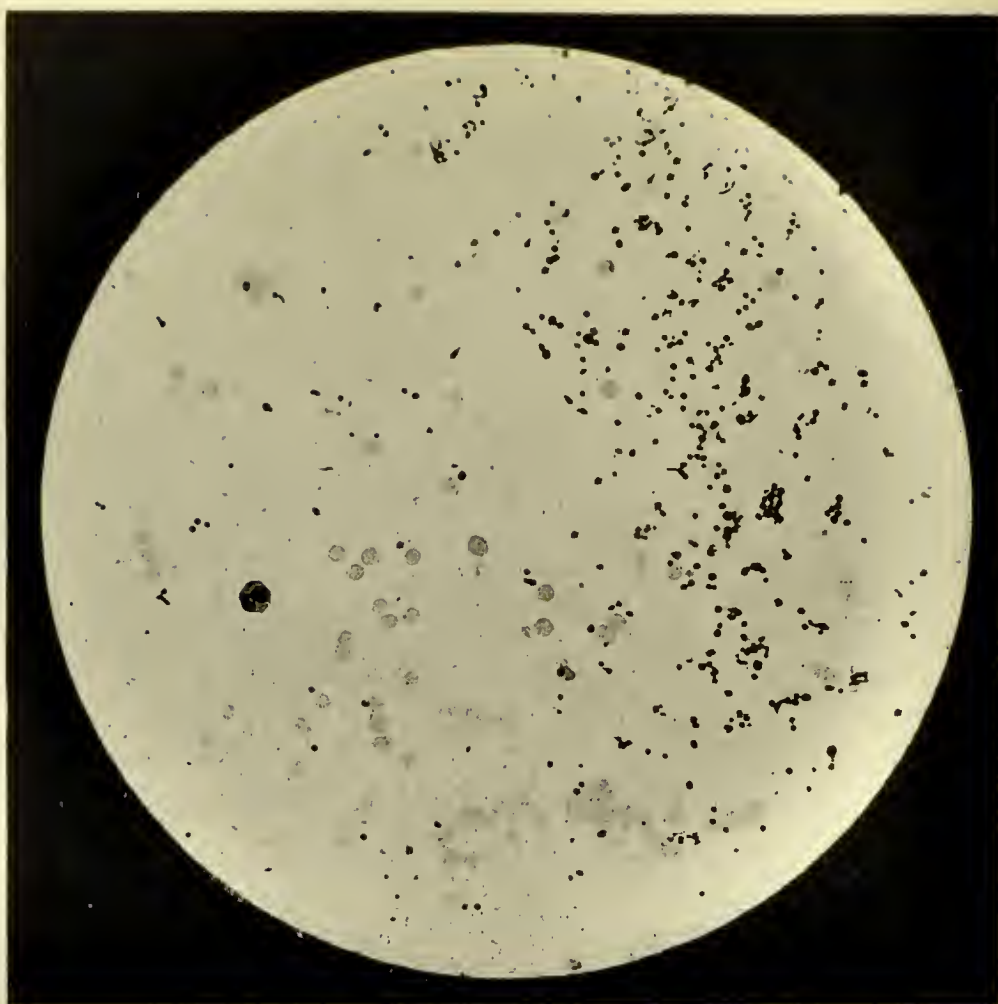


Fig. I.
Normal blood. Blood plates. Zeiss A.

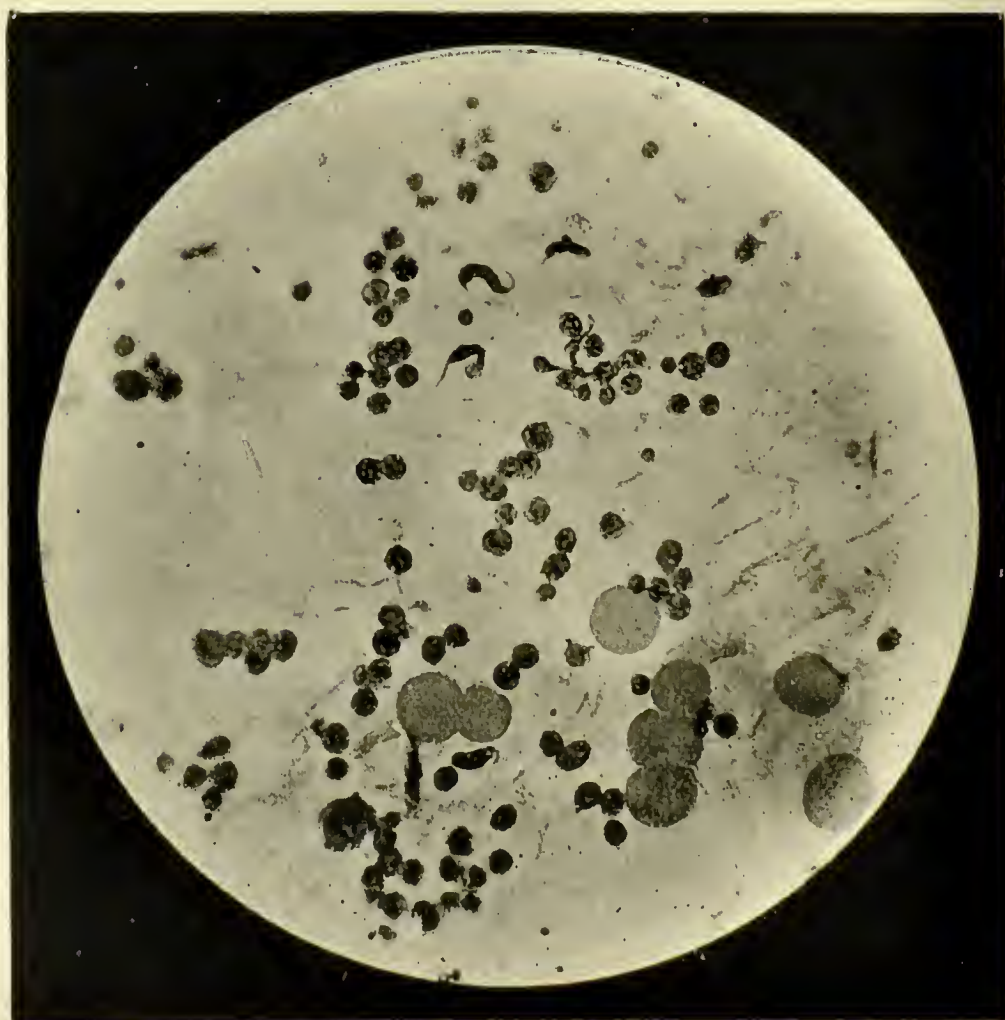


Fig. II.
Normal blood. Red cells and platelets.

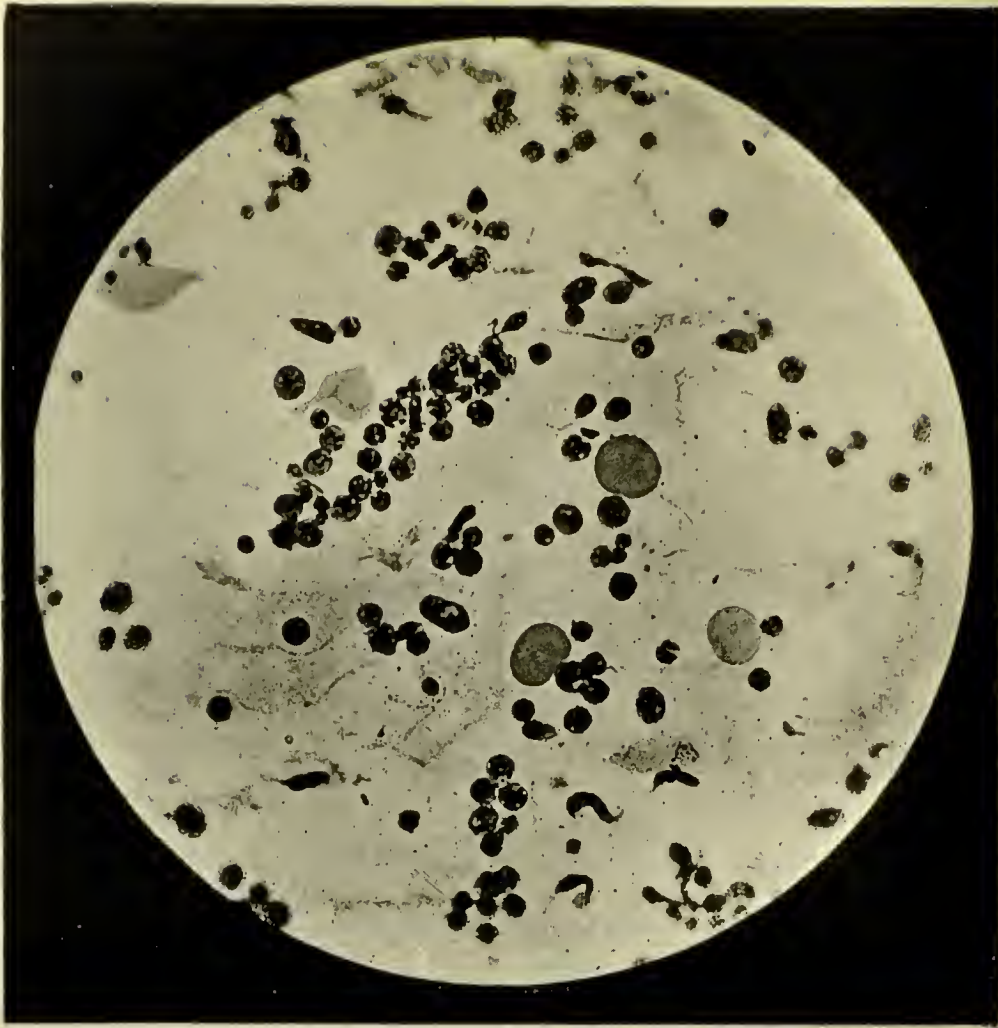


Fig. III.
Normal blood. Red cells and platelets.

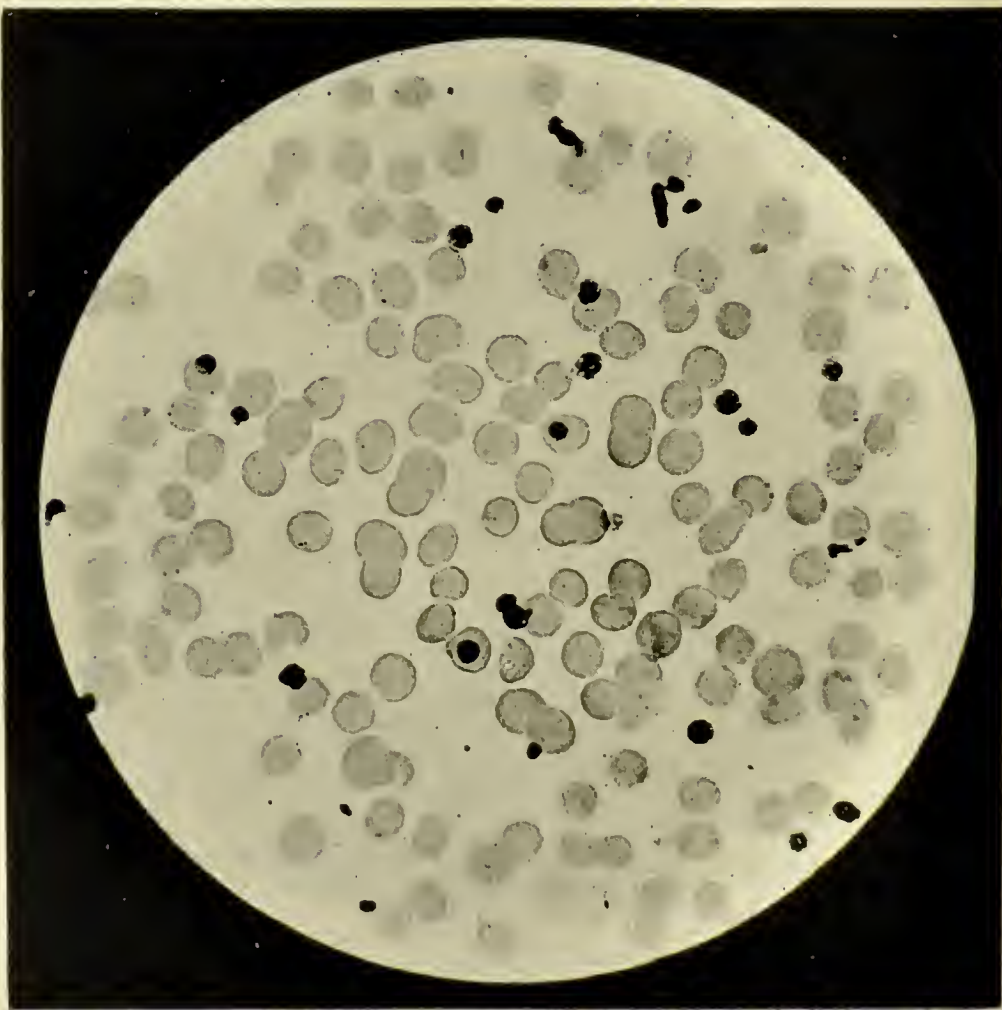


Fig. IV.
Normal blood. Platelets in, or being extruded from red cells.

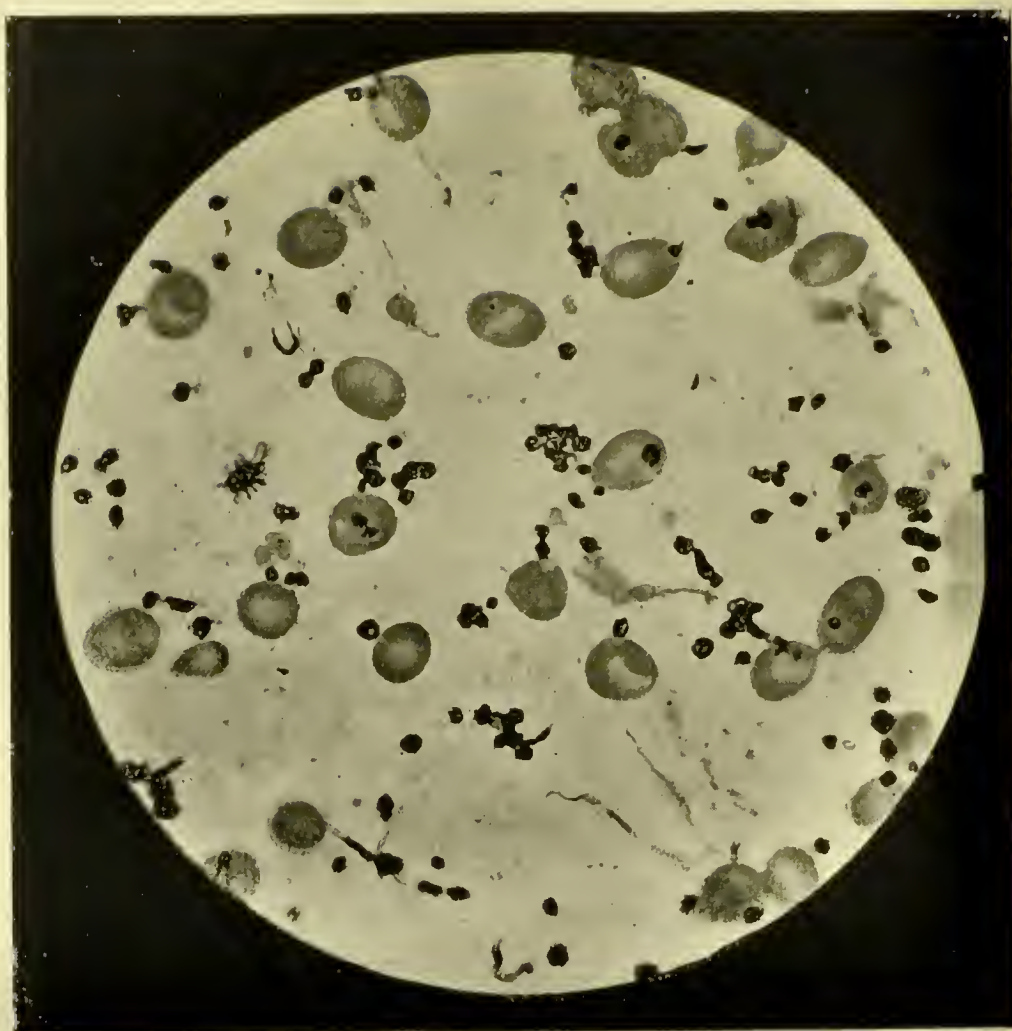


Fig. V.
Pernicious anæmia (?). Red cells and platelets.

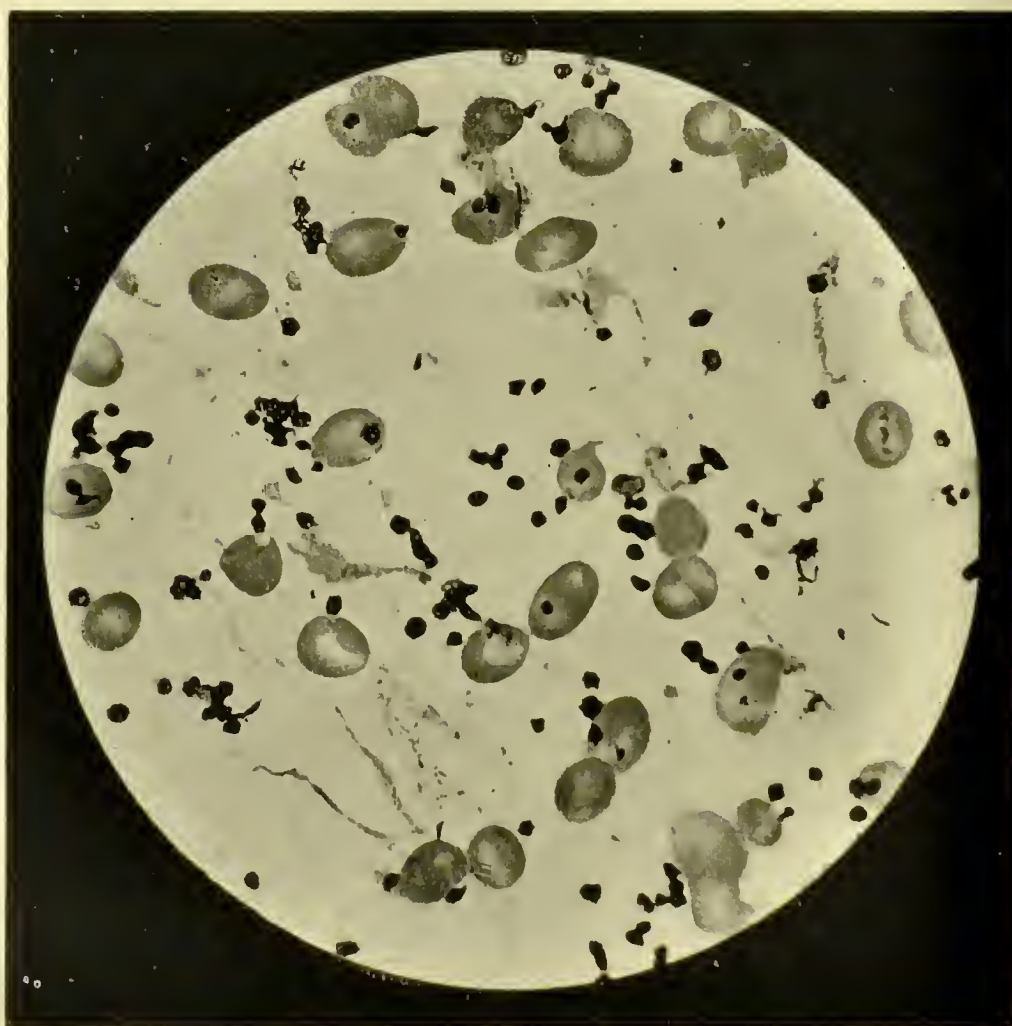


Fig. VI.
Pernicious anæmia (?). Red cells and platelets.

Characteristics of the Platelets.

The characters of the well-formed platelets seen in these slides are very distinct. They appear as *discrete*, cellular-looking structures, about half the size of a red cell (Figs. 1—4), with as a rule distinct circular outline. Occasionally they are more oval, and in some instances tailed and flagellate, and very suggestive of trypanosomes to the uninitiated. They consist of (1) a clear structureless hyaline body which either does not stain at all, or else which takes a faint bluish tint; (2) chromatin granules often aggregated into one or two nucleus-like bodies, of irregular outline and without the distinct limitations of the nucleus of a red or white cell, which take a mixed eosin and blue stain of varying depth of colour; (3) vacuoles, in the middle of chromatin masses. These may be vacuoles or only collections of the hyaline substance of the platelet.

In smears made on a warmer slide the platelets appear as above, and often in profusion in that part of the smear where the blood was originally in contact with the slide before the smear was made. In some of my slides they form a streak across the film which is quite visible under the A lens of a Zeiss microscope (Fig. 1).

The platelets have great adhering power in contact with glass, perhaps even better than that of red corpuscles, for they alone are often seen in that first part of the smear where they are best found, the red and white cells occupying the adjoining parts of the slide. In addition to the large numbers of platelets which are seen on the slide, careful observation will reveal the presence of several red cells with what, to a superficial glance is a weakly-stained nucleus in their substance (Figs. 4, 5 and 6). In some instances two smaller chromatin masses may be seen in a red cell. These structures are very important, for they are red cells containing blood plates, fixed and stained just as the latter are being extruded from the red cells, which, I hope to prove, give rise to all the bodies which I am describing as blood plates.

Staining Characteristics of the Platelets.

Leishman's stain. The red cells take the eosin, the white cells and their nuclei the blue, but the chromatin of the platelets

takes a distinct lilac-purple shade when stained for five minutes, and a deeper purple when stained for a longer time. The contrast of the staining of the platelets with that of the red cells is very marked when one of the former is stained in the red cell. The body of the completely formed platelet may take a faintly bluish tinge, and the depth of the chromatin stain depends on the degree of aggregation of the granules and the length of time occupied by staining. As I have already stated, the chromatin may appear as dark, nucleus-like masses of a deeper purple colour, the less densely packed granules being a lighter shade. When the platelets are collected in large confluent masses of their chromatin constituent the appearance is that of collections of purple-staining material of irregular outline and shape.

That a platelet in a cell body is not a nucleated red cell is very definite. The platelet does not take the intense blue stain of a true nucleus, it is not so compact in structure, nor has it the mitotic-like appearance which the nuclei of many red cells show.

Ehrlich's acid hæmatoxylin and eosin. When a smear is fixed with acetone-free methyl alcohol or by heat, as by passing through the flame of a bunsen-burner and then stained, the platelets do not take the stain well, their structure not being differentiated clearly, but forming a dull, indistinct body. This fact shows that they are not of the material which forms the nuclei of red cells.

Origin of the blood plates. (1) Do they exist preformed in the blood? (2) Do they arise from the red cells, (3) from the white cells, (4) or from the plasma? The evidence which I have obtained points, I submit, conclusively to the red cell origin of the platelets, and therefore I will refer to it in the first instance.

In slides made as I have described platelets are to be seen in more or less numbers either lying outside and on the proximal surface of a red cell, where it has arrived by a coincidence, or else lying within the cell and on the point of being, or having just been, extruded from it. I have no doubt that the latter condition is what really exists, and for the following reasons:—

1. It is quite common, as many previous observers have stated, to see in normal blood a small cluster of three, four or half a dozen platelets lying together in the mouth of a gaping,

burst red cell. Their appearance is unmistakable, and, in my opinion, is so obvious as to admit of no doubt that the platelets are the extruded contents of the burst red cell. Such platelets have not the cellular structure of those which are more complete in form. They are without the clear ground substance, and consist of chromatin only.

2. Careful focussing, with an oil immersion $1/_{12}$ Zeiss lens, of the platelet on or in a red cell points to the "inside" theory.

- (a) The platelet is not out of focus when the red cell is in focus.
- (b) The whole contour of the platelet is not distinct, its periphery being indefinite.
- (c) That portion of the red cell which immediately adjoins the platelet takes the eosin stain less markedly than the rest of the cell, and suggests such thinning of the stroma as could be accounted for by the platelet and red cell being fixed just as the former is bursting through the latter and displacing the eosin-staining tissue of the red cell.
- (d) Not uncommonly a platelet is seen apparently partly extruded from part of the periphery of a red cell.
- (e) Not uncommonly a platelet is seen deeper in the red cell, taking the stain much more lightly than when nearer the surface.
- (f) In those smears which are made on a hot slide, there are more platelets in or on the red cells than in those made on a slide at the temperature of the atmosphere—I suggest because the greater heat has fixed the red cell quickly and caught the platelet escaping. When the blood is on a cold slide the platelet has time to get out before the forces which cause its extrusion cease to act with the death of the red cell.
- (g) In some diseases, notably the case from which two of my figures is taken (pernicious anæmia), very many red cells show the chromatin mass in their substance.
- (h) In some instances the extruded platelet may be completely outside the red cell when it will focus differently to the red cell.

Actual fragmentation of a red cell gives quite a different appearance. Such a condition is seen best if a smear be made on rather a hot slide (about 110°F.). When a smear is made on a slide at the temperature of the room the force which makes the smear distorts the red corpuscles, which are highly elastic bodies, but there is plenty of time after the cessation of the smearing force for the red cell to regain its disc-like shape. When, however, the slide is hot the smear is made quickly, and there is no time for the distorted red cell to regain its original shape before it is killed. In such a slide the red cells are seen as streaks about twice the length of the diameter of an ordinary red cell and about as wide as a red cell when seen on end. Small pieces of red cells, apparently pulled off in the process of making the smear, and looking like microcytes, are also plentiful, and these all stain like the red cells, and have no resemblance whatsoever to a blood plate.

All this positive evidence tends to exclude the possibility of the platelet being formed from fragmentation of a white cell or from extrusion of any of the contents of a white cell. Moreover, I have never seen anything to suggest that this does occur. It also tends to prove that the platelets do not develop from the plasma. Again, I have seen nothing that bears out this suggestion. It also tends to prove that the platelets do not exist pre-formed in the blood. As further evidence against this theory is the fact that the platelets appear in very much greater numbers in blood which has been allowed to stand 30 seconds before smearing than they do when the smear is made as soon as possible after the blood touches the slide.

What determines the formation of Blood Platelets?

This may be one of several causes—(1) contact of the blood with a puncturing instrument; (2) with the skin at the seat of puncture, or (3) with the glass of the slide; (4) the change of temperature incident to the passage of the blood from the capillaries into the air of the laboratory; (5) or to the action of the gases of the air.

(1) *Puncturing instrument.* That this is not the cause of the formation of the platelets is proved by the fact that more platelets

form the longer the drop of blood has been allowed to stand, within the before-mentioned limits of time, in contact with the slide. At the same time, there is no denying the possibility that the original entrance of the instrument into the capillaries may, either by the rupture of some blood elements or by some other action, have released some ferment or substance which has the power of inducing the further formation of platelets in the drop of blood on the slide. But I have no evidence to offer in support of this possibility.

(2) *Contact with the finger.* The natural secretions or excretions of the skin or dirt on the finger might be the determining cause, but

(a) Cleansing with ether, alcohol, soap and water before the puncture, makes no difference in the number of platelets which are formed as compared with the results of puncturing a finger which has been merely washed with soap and water.

(b) If a smear be made within a second or two of the puncture, or after the blood has remained 10—20 seconds on the finger, the number of platelets formed under the conditions described originally is the same whether the finger has been made aseptic, or only washed with soap and water.

(3) *Contact with the glass of the slide* probably has some influence on the formation of the blood plates. This is suggested by the large numbers which are to be seen on that part of the slide on which the drop of blood rests before it is smeared.

(4) The *change of temperature* may have something to do with the formation of the platelets, but my observations with a slide warmed to the body heat suggest that the cold of the atmosphere rather tends to a slow formation of the blood plates.

(5) *Contact with the gases of the air*, apart from the temperature, probably has some action on the extrusion of the plates from the red cells. But the process goes on when the atmosphere is practically prevented from acting on the blood cells. Thus if two closely applied square cover-slips be placed over the seat of puncture, one corner dipping actually into the puncture, and blood be allowed to diffuse up between them

through capillary action, the platelets still form. Here, however, there is probably some air in contact with the blood, even if it be but a slight amount.

Is the material from which Blood Plates are formed in every Red Cell or only in some?

My observations suggest that only a certain number of red cells contain the material because the number of platelets formed in a slide does not seem to be equivalent to that of the red cells present. This is, however, a difficult point, and one which is now engaging my attention.

Why are the platelets seen only, or in such profusion, on that part of the slide where the droplet of blood has stood before smearing? Does it mean that whilst the blood has been standing there more red cells have settled down and come in contact with the glass and have met with those physical conditions which bring about their formation? Against this view is the fact that if a smear be made at once so that nearly all the red cells in the drop of blood come in contact with the glass and air whilst alive there are comparatively few platelets to be found on the slide. I have kept a smear made in this way moist for 10 or 20 seconds so as to allow time for formation of blood plates, but without any definite result. Again, with such large numbers of red cells as are contained in a drop of blood it is conceivable that all of the red cells could not come into relation with those physical conditions which determine the extrusion of the blood plate, but the evidence just afforded above is also against this conception.

What happens to a Red Cell after it has given rise to a Blood Plate?

As far as its staining characteristics go the cell is apparently none the worse for its loss of the substance which forms the platelet. Cells with a platelet just appearing take the eosin stain as well as ever, and those which have burst in parting with their platelet material are as well stained as any other red cell in the field.

Do Platelets contain Hæmoglobin?

No; because if a smear be treated with distilled water before fixing to remove the hæmoglobin, whilst the red cells will not take their acid stain afterwards, the platelets take their mixed stain as usual. Such an observation is best carried out by making a smear, letting it dry and then passing it slowly through a bunsen flame to partially fix it. When this is gently treated with distilled water the red cells disappear to the naked eye. If the slide be gently dried, then stained with Leishman's stain in the ordinary way and examined, the red cells are found to be colourless, but the platelets have stained very well. The half fixing of the smear makes it stand the distilled water without losing its cells.

Are the Bodies which I describe Artefacts?

Certainly not, if by the word artefact is meant something manufactured by the art of the observer. They are made in the natural order of events by certain physical forces acting on the red blood cells which cause the extrusion of materials composing the platelet. In my observations no chemicals, such as are contained in Deetjen's, Wlassow's or other fluids were used, my whole endeavour having been to preserve intact the delicate structures which are derived from the red cells when the latter come into association with these physical forces which determine the formation of the blood plates. The use of a cigarette paper brings less force into play in making a smear than does the employment of a glass slide for making the smear, and results, I believe, in leaving more of the delicate material which forms the body framework of the platelet than a glass slide does. The fact is that platelets are found to be better formed after the use of the cigarette paper than after the use of the more rigid glass.

I have seen nothing to suggest that the platelets are formed by the rolling into spherical masses of materials from the plasma of the blood.

A blood plate, then, is formed by the escape of the normal component parts of a red blood corpuscle, and the method of their extrusion, and their appearance when extruded appear to

me to suggest that they form the central core of a red corpuscle and are surrounded by an outer covering which consists of a stroma containing the hæmoglobin of the corpuscle. Whether the material for their formation exists in certain red corpuscles only or in all is not evident at present.

APPEARANCES IN VARIOUS DISEASES.

Chlorosis. In slides made as I have described blood plates appear in extraordinary numbers, and many are to be seen in the parent red cell.

Pernicious Anæmia forms a marked contrast to chlorosis, blood plates being remarkably few or absent altogether in most cases. In one case of apparently typical pernicious anæmia, however, I found many platelets by working with hot slides (see Figs. 5 and 6).

In one case of Splenic Anæmia—probably Banti's disease—which I had under my care, blood plates were practically absent.

Lymphatic Leucocythæmia. In one case which I examined the plates were very scanty.

Platelets occur in large numbers in most secondary anæmias, in spleno-medullary leucocythæmia, acute and chronic Bright's disease, and many other conditions.

PATHOGENIC PROPERTIES OF AND AMOUNT OF DIRT CONTAINED IN THE MILK SUPPLIED TO THE TOWN OF MANCHESTER DURING THE TEN YEARS 1897 TO 1906 INCLUSIVE.

By SHERIDAN DELÉPINE, M.B., C.M., M.Sc., *Director of the Public Health Laboratory, and Professor of Comparative Pathology and Bacteriology, Victoria University of Manchester.*

IN the course of the past 15 years I have utilised the samples of milk which were sent to my laboratory (for the purpose of determining whether they contained tubercle bacilli), to investigate as accurately as possible the relation between the state of the milk supplied to towns and the production of disease. Since 1895, some 7,120 samples of cows' milk have been examined bacteriologically in my Laboratory, by myself and Dr. F. J. H. Coutts, Dr. E. J. Sidebotham or Dr. A. Sellers, according to the methods which I adopted at the beginning, and which have been adhered to up to the present day.

Systematic records have been kept since 1896 of the reaction, amount of sediment separable by centrifugalisation, and of the kinds of extraneous products, cells, and bacteria composing the sediment. Two guinea pigs have in each case* been inoculated, each with the whole of the sediment obtained from 40 cc. of milk. The effects of the inoculation have been carefully noted both in the case of animals dying spontaneously and of those that were killed after a period of several weeks. In many cases the lesions observed post mortem were clearly connected with the inoculation, in a few cases the lesions were accidental.†

In all cases where lesions were found at the seat of inocula-

* Except in a very few cases where only one guinea pig was used.

† All the accidental or doubtful results have been eliminated from the laboratory statistics.

tion and in the lymphatics connected with the seat of inoculation, or when both animals died about the same time, and exhibited general and local lesions of the same kind, the diseased state was attributed to the milk. I need not say that I have taken the utmost care to secure sterilization of all the apparatus used in connection with the inoculations, and that I have repeatedly tested the efficiency of the methods adopted.

These records constitute a body of scientific evidence based on a very large number of experiments made in the course of over 13 years.

In analysing these data for the purpose above stated, I have found very clear evidence that a great improvement has taken place in the Manchester milk supply in the course of the last 11 years.

During the 10 years 1897 to 1906 inclusive, 4,596 samples of milk have been sent to my laboratory by the Public Health Department of Manchester. Of these, 3,650 have been collected either at railway stations or at places away from the farms. These samples therefore represent the *milk which has during these 10 years been supplied to the Manchester consumers*. They were all samples of what I call mixed milk, and not samples of milk obtained from single cows, or small groups of cows examined at the farms.

Among these samples of mixed milk there were samples taken for the purpose of controlling the efficiency of previous inspection. The number of these samples varied from year to year, and this may have affected slightly the yearly percentages of tuberculous milk. These variations are, however, slight. On the other hand, it is obviously advantageous to take into consideration all the milk that was put upon the market.

If all these samples of mixed milk are classified according to the lesions which they produced in guinea pigs inoculated with them, it is found that in the years 1897 and 1898* not less than 45 per cent produced some kind of lesion, while in 1906 the percentage had fallen down to 14·4.

* No mixed milk samples were taken in 1899

If instead of grouping all the lesions together one takes only tuberculosis in account, the change is not less striking, for in 1897-1898 the number of tuberculous samples was 17·2 per cent., while in 1906 it had fallen to 6·6 per cent.

The same improvement is shown with regard to severe septicæmic lesions causing the death of one or both animals in less than three days. In 1897-8, 3·6 per cent. of the guinea pigs suffered from such lesions, but *since 1902 no case of this kind has occurred.*

I have prepared a table and diagram showing the yearly results, and it will be noticed that between the years 1897 and 1902 a rapid improvement had taken place. This improvement was followed during the years 1902 and 1903 by a slight relapse. This relapse is attributable to several causes. One of these causes is possibly the impression which the statements made by Professor Koch at the Congress of Hygiene in 1901 had on farmers and agriculturists. I noticed that soon after that Congress many persons interested in the dairy industry expressed contempt for the measures which were taken against tuberculosis in cattle, and some assumed a very defiant attitude. Another possible cause may have been the inclusion of new districts in the field of inspection work. This is the most probable explanation. Whatever was the cause of that short relapse, it was followed by a period of continuous improvement, which has now lasted four years. But even in 1903—*i.e.*, at the time when there appeared to be an arrest in the progress—the number of tuberculous samples reaching Manchester had already been reduced to two-thirds of what it was in 1897-8, whilst in 1906 it had fallen to nearly one-third of the original number. *Not only has the number of tuberculous samples diminished, but the lesions produced by them in inoculated animals have become slight when compared with those observed at the beginning of this inquiry.* This fact shows that the lesions of the tuberculous udders producing tuberculous milk at the present time are much slighter than those which were prevalent 10 years ago.

The work of inspection has had another and a wider effect which can be estimated by comparing the amount of dirt and other abnormal products that can be separated from milk.

The sediment separated by centrifugalisation consists of :—

1. *Cells* derived from the internal and external parts of healthy and diseased udders (*e.g.*, catarrhal products, pus and blood), and from the hands of the milkers.

2. *Hairs* derived from the skin.

3. *Wool and cotton* from clothing, strainers, and other articles.

4. *Vegetable and mineral* matter derived (*a*) from food dung, litter, dirt clinging to the skin of the cow or the hands of the milker; also (*b*) from the water used for cleaning cans and other vessels. The water is also the source of the algæ which are sometimes present in the sediment.

5. *Animalcules*, such as infusoria, worms, insects, and arachnides coming from the food, litter, water used to clean vessels, and possibly from the hands and clothing of dirty milkers.

6. *Pathogenic and saprophytic bacteria, yeasts, and moulds* from various sources.

It is therefore reasonable to expect that the amount and character of the sediments (commonly called slime) which are separable from samples of milk will vary according to the state of the cow-sheds and dairies, and that when the cows, cow-sheds, milkers, dairies, dairy-vessels, and water used for cleaning and other purposes are clean, the amount of sediment will be smaller than when reverse conditions exist.

I have therefore paid special attention to the amount of sediment obtainable from all the samples which have been submitted to me, in the hope that this might yield useful results.

The appended Table II. gives only the gross results of this investigation. The amount of dirt, etc., has been estimated by measuring the diameter of the sediment deposited in tubes of uniform diameter, containing each 40 cc. of milk, and left for a quarter of an hour in a centrifugal machine running at the rate of about 2,500 revolutions per minute. The absolute amount of sediment is not indicated by these measurements, but I have

estimated approximately the relation between the diameter and the weight of these sediments.* A diameter of :—

6-8 m.m. corresponds to about 7 to 14 grains of dense moist slime per gallon.

9-10	„	„	20 to 42	„	„
13	„	„	40 to 84	„	„
15	„	„	80 to 175	„	„
16	„	„	130 to 260	„	„

To control these results, I weighed the slime separated from 15 gallons of average milk such as reaches the town. This material was kindly supplied to me by Mr. Hailwood in 1900. I found that the amount of moist slime separated from 15 gallons of milk was in this case 304.45 grains, *i.e.*, about 20 grains per gallon. This amount corresponds, therefore, to 9 to 10 m.m. of my scale. During that year more than half of all the samples of milk collected in Manchester yielded sediments from 9 m.m. to 20 m.m. in diameter. It will be seen that the *lower* estimate of the weight of sediment corresponding to 9-10 m.m. may be taken as giving approximately the amount of dirt and cellular constituents of which the sediment is composed, 20 grains being the probable average in 1900.

The quantity of milk reaching Manchester in 1900 was estimated at about 30,000 gallons per day; the amount of slime supplied daily to the consumer was therefore about $\frac{30000 \times 20}{7000} = 85$ lbs.

Taking the average of the last 10 years as my basis, I have come to the conclusion that samples of milk yielding sediments measuring less than 9 m.m. in diameter might be considered to be as *clean* as is practically possible, and that samples with sediments measuring not more than 7 m.m. were *very clean*. Samples with sediments measuring from 9-10 m.m. should then be considered of *doubtful cleanness*. Sediments above 10 m.m. indicate an *excessive amount of dirt*, or in some cases the presence of an unusual number of *cells presumably derived from diseased udders*.

* *i.e.*, of moist sediments, to obtain accurate estimates it would be necessary to dry these sediments. The amount of moisture retained depends on the speed and diameter of the centrifugal disc as well as on the duration of the operation. The figures given here are comparable among themselves.

I wish, however, to emphasize the fact that there is no constant relation between the amount of dirt and the pathogenic properties of the milk. Some milk containing a large amount of slime appears to have no pathogenic effect on experimental animals, and on the other hand many samples of milk containing a small amount of slime are highly infectious.

It must therefore be clearly understood that I look upon the *amount of slime only as an indicator of the care which has been taken in the keeping of the cows, and in the collection and distribution of the milk.* I may say that I have observed the same discrepancy between the number of bacteria and the pathogenic properties of the milk. I will, on some future occasion, deal with this aspect of the question to which I have already alluded in some previous communications.

But although there is no constant relation between the amount of dirt and the pathogenic properties of the milk when individual cases are considered, there is a distinct *average correlation between the amount of dirt and the pathogenicity of milk*, and the tables will show clearly that the reduction in the amount of dirt found in the milk supplied to Manchester during the past ten years has been associated with a marked diminution in the number of samples capable of producing disease in inoculated animals.

In order to have a sufficient number of samples as a basis for the calculation of percentages, I have been obliged to group the years 1897, 1898, and 1900 together.* For the same reason I have grouped the years 1901 and 1902, and 1903 and 1904 together. In this way I have obtained five periods—1897 to 1900 with 454 samples, 1901 and 1902 with 861 samples, 1903 and 1904 with 867 samples, 1905 with 764 samples, and 1906 with 704 samples. I have not been able yet to work out the results obtained in 1907, but I am under the impression that they show a further improvement.

With regard to the amount of sediment, it will be noticed that, as in case of pathogenic effects, there was about the years 1902 and 1903 some interruption in the rate of improvement.

* No samples of mixed milk were submitted to me in 1899.

The number of samples of doubtful purity, which in 1897—1900 was about 60 per cent., had fallen to about 40 per cent. in 1901—2, and rose to 45 per cent. in 1903—4; since that period there has been a rapid fall down to 30 per cent.

With regard to the dirty milks, there has been an almost uninterrupted fall from the beginning. In 1897—1900, the average number of these milks was 12·5 per cent. In 1906 it had been reduced to less than 5 per cent. The number of very dirty milks had been reduced during the same period from $2\frac{1}{2}$ per cent. to $\frac{1}{2}$ per cent., *i.e.*, from 5 to 1.

For an account of the methods I have devised or adopted in carrying out this work, I must refer the reader to my previous publications on the subject, more especially to the following:—

“On the value of experimental tuberculosis in diagnosis.”

Brit. Med. Journ., 1893.

“Spread of tuberculosis through the lymphatics.” *Brit. Med.*

Journ., 1894; *Med. Chronicle*, 1894.

“The examination of cow’s milk for the detection of pathogenic properties.” *Journ. of Comp. Path.*, p. 150, 1897.

“The examination of cow’s milk for the detection of tubercle bacilli.” *Transactions of the Aberdeen Congress of the Royal Inst. of Public Health*, p. 221, 1900.

Regarding the dangers associated with the consumption of tuberculous or polluted milk, and the need of more stringent administrative measures than those in force, some information will be found in several contributions which I have written from time to time, *e.g.*,

“Tuberculous infection through the alimentary canal.” Address delivered to the Medico-Ethical Society, Manchester, 1892. *Med. Chronicle*, 1895.

“Prevalence of tuberculosis in the domesticated animals.” *Med. Chronicle*, 1895.

“Desirability of legislation in connection with tuberculosis of living domesticated animals, and more especially of cattle.” *Journ. of State Medicine*, 1896.

"Tuberculosis and the milk supply, with some general remarks on the dangers of bad milk." *Lancet*, 1898.

"The prevention of tuberculosis." *Public Health*, 1899.

"Prevention of tuberculosis in cattle, some economic aspects of the question." *The Veterinarian*, 1899.

"The stamping out of bovine tuberculosis, with remarks on the relation of bovine to human tuberculosis." *Transactions of the British Congress on Tuberculosis, London*, 1901.

"Communicability of human tuberculosis to cattle." *Brit. Med. Journ.*, 1901.

"The bearing of outbreaks of food poisoning upon the etiology of epidemic diarrhœa." *The Journal of Hygiene*, 1903.

These references are given here for the purpose of indicating the scope of the work related to the present communication, a complete bibliography of the subject would occupy a considerable amount of space.

Diagram I. — 3650 SAMPLES OF MIXED MILK COLLECTED IN MANCHESTER 1897-1906
ARRANGED ACCORDING TO LESIONS PRODUCED IN GUINEA PIGS BY INOCULATION.

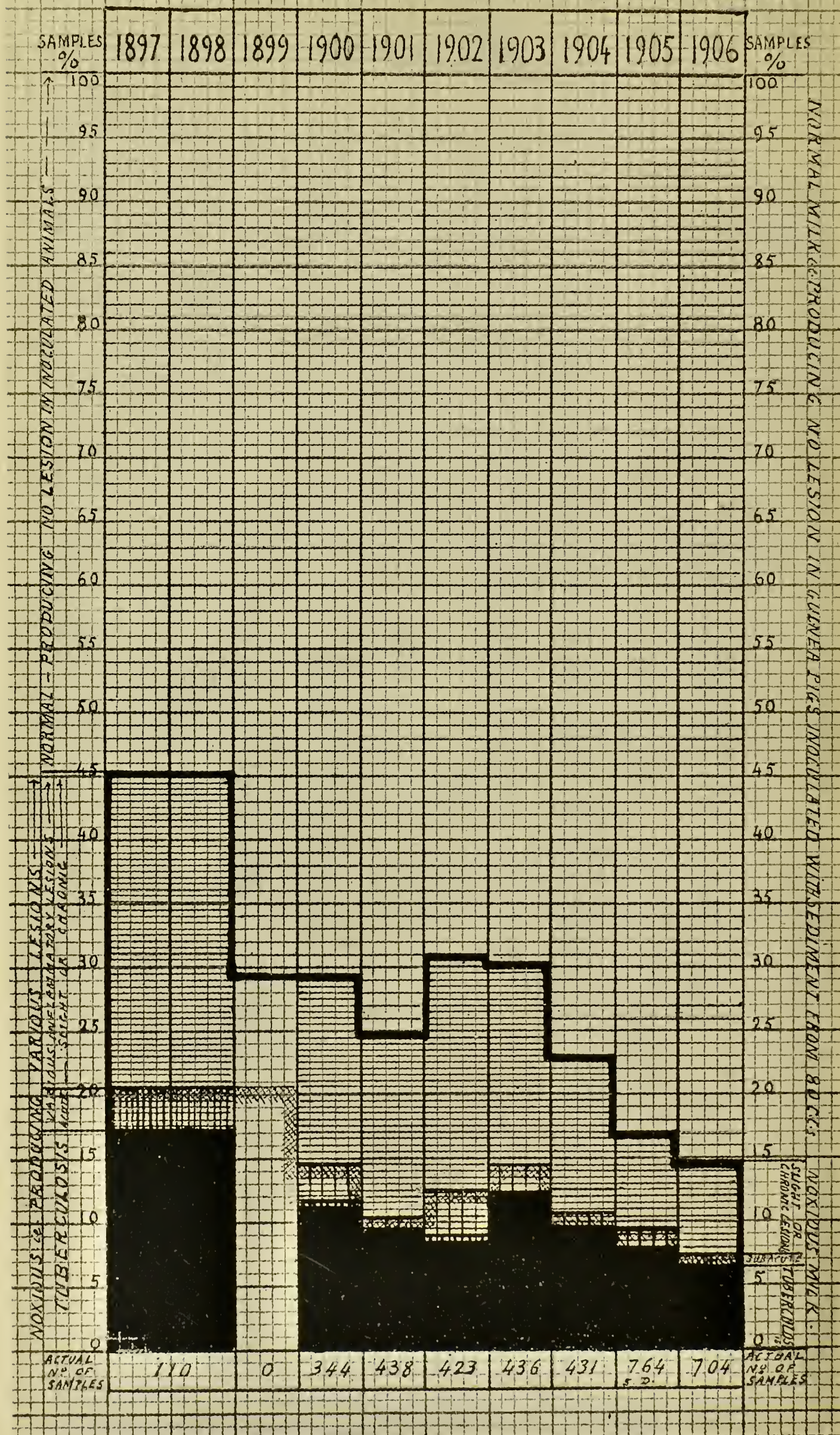


Diagram II. 3650 OF MIXED MILK COLLECTED IN MANCHESTER - 1897 - 1906
ARRANGED ACCORDING TO THE AMOUNT OF SEDIMENT SEPARATED FROM 40 C.C.

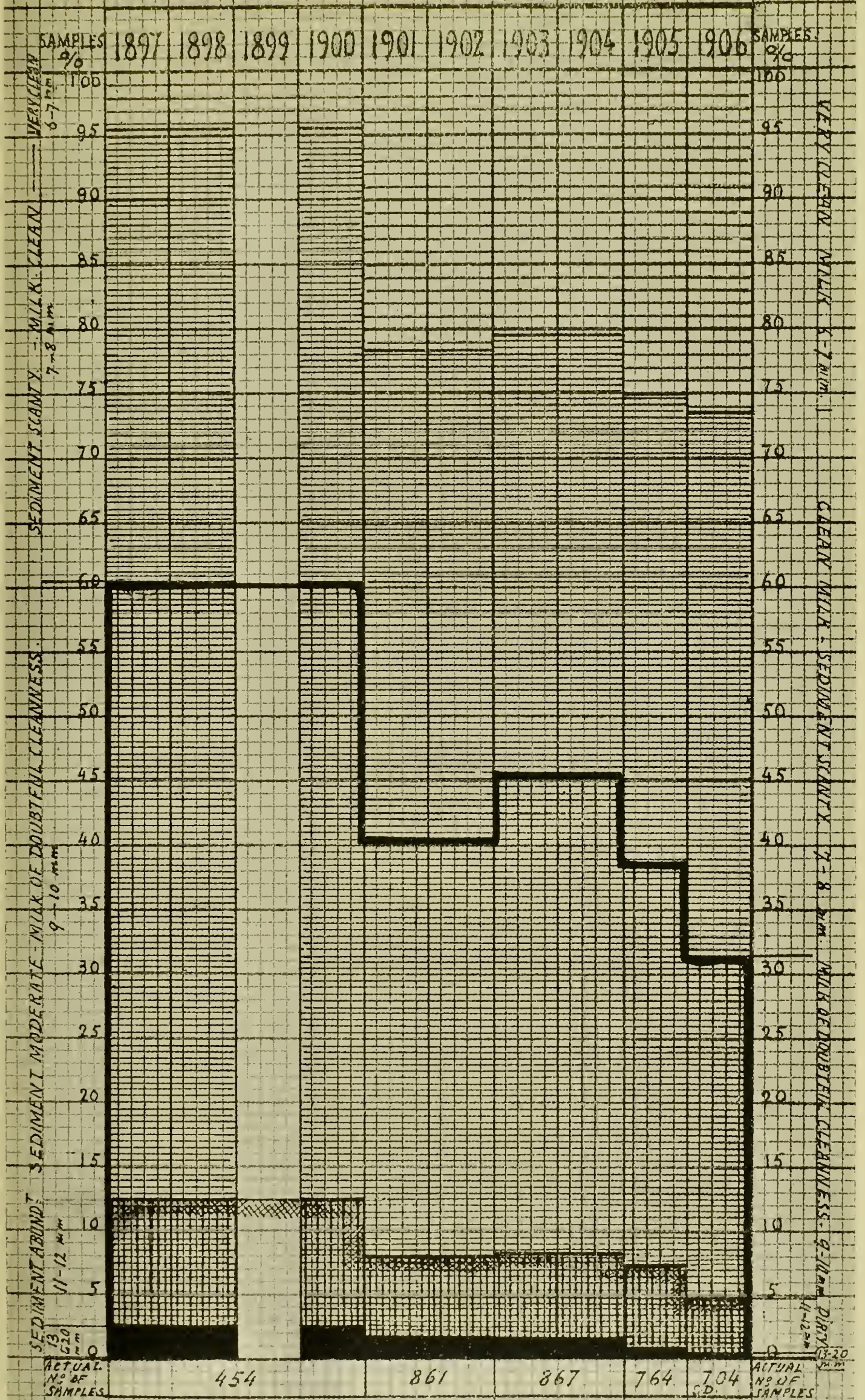


TABLE I.—RESULTS OF INOCULATION OF GUINEA PIGS WITH THE SEDIMENT OBTAINED FROM 40 C.C.'S OF MILK IN EACH CASE.

MANCHESTER.—Mixed Milk taken at Railway Stations and other places away from the Farm—i.e., Milk such as would have been supplied to the consumer in Town. In this table of gross results control samples are included.

YEAR	GROUP I. Normal		GROUP II. Chronic		GROUP III. Sub-acute		GROUP IV. Acute		GROUP V. Tuberculous		Actual Number of Specimens Examined	REMARKS.
	Actual Number	%	Actual Number	%	Actual Number	%	Actual Number	%	Actual Number	%		
1897-8	60	54.5	27	24.5	4	3.6	19	17.2	110	GROUP I.—Normal—No lesions observed attributable to milk.
1900	243	70.5	50	14.5	10	2.9	2	0.6	39	11.3	344	GROUP II.—Chronic—Evidence of various forms of inflammation, not fatal or very slowly fatal, and clearly attributable to milk.
1901	329	75.0	64	14.6	3	0.7	42	9.5	438	GROUP III.—Sub-Acute — Various lesions attributable to milk, and fatal to one or both animals from 4 to 10 days after inoculation.
1902	292	68.0	78	18.4	15	3.5	2	0.47	36	8.5	423	GROUP IV.—Acute—Lesions attributable to milk and fatal to one or both animals within 3 days.
*1903	303	69.4	70	16.0	9	2.0	54	12.3	436	GROUP V.—Tuberculous lesions.
1904	331	76.7	53	12.2	5	1.1	42	9.7	431	
1905	633	82.8	58	7.5	12	1.5	61	8.1	764	
1906	601	84.7	50	7.0	6	0.8	47	6.6	704	
											3650	

* During this year a number of farms which had not previously been inspected were included in the operations.

TARLE II.—AMOUNT OF SEDIMENT SEPARATED BY CENTRIFUGALISATION.

MANCHESTER.—*Mixed Milk taken at Railway Stations, or at other places away from the Farm.*

YEARS	CLEAN MILK				DOUBTFUL		MILK CONTAINED MARKED EXCESS OF DIRT OR ABNORMAL PRODUCTS.				TOTAL
	Under 7 m.m.		7-8 m.m.		9-10 m.m.		11-12 m.m.		13-20 m.m.		
	Actual No.	%	Actual No.	%	Actual No.	%	Actual No.	%	Actual No.	%	
1896-1900	19	4.2	160	35.2	218	47.9	45	9.9	12	2.6	454
1901-1902	186	21.5	325	37.7	280	32.5	53	6.1	17	1.9	861
1903-1904	164	18.9	295	34.0	326	37.5	57	6.5	15	1.7	867
1905	190	24.8	276	36.1	242	31.6	49	6.4	7	0.9	764
1906	185	26.2	296	42.0	188	26.7	31	4.4	4	0.5	704
											3650

The numbers indicating the amount of sediment show only the relative amount. The absolute amount of sediment is not given in this table.



